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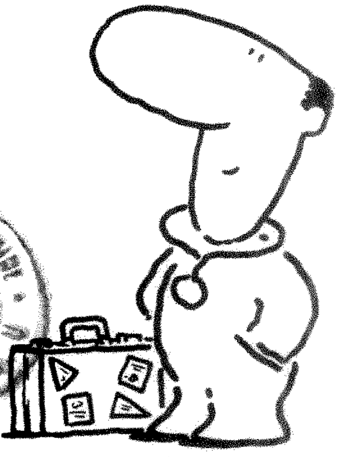

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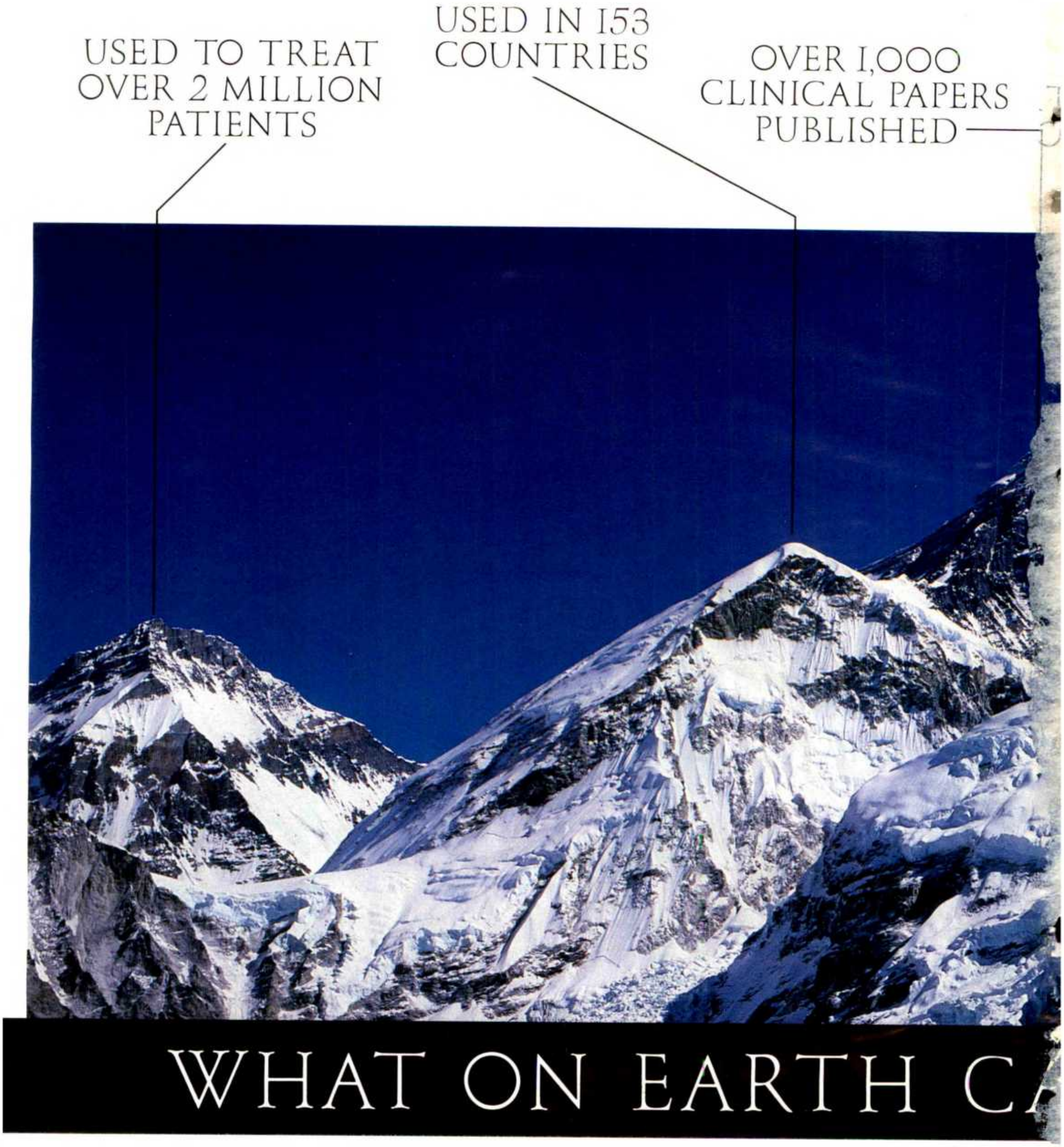
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*British Journal of Ophthalmology*, 1991, 75, 385

BRITISH JOURNAL OF
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## *Editorial*

# Laser beam clipping: two aspects and a safety device

In this issue we publish two different aspects of the laser beam clipping problem. To those of us who perform a modest amount of laser work the irritation of periodic apparent failure of the laser to act is soon explained by some kind and more experienced colleague as beam clipping. For those who find the phrase obscure it may be expressed in more familiar terms as something getting in the light. Beam clipping occurs in circumstances other than lasering. It happens, for example, when we look into another person's eyes and see their pupils black. This is because our own head has beam clipped, not to say beam blocked, the rays of light entering the pupil which are needed to enable us to view the retina. This state of affairs is avoided by the device of a mirror with a hole in it in the direct ophthalmoscope or by the subtler approach of throwing a real image of the pupil into space in front of our own eyes, as in the various indirect systems. As explained in the papers from Woon *et al* and the letter from Moseley *et al* in the present issue, several forms of beam clipping are possible during the use of therapeutic lasers.

Iris clipping, which is dealt with in the paper by Woon *et al*, is not something which would be immediately obvious, and thus we are grateful to the authors for bringing it to our attention. The essence of it is a disproportion between the cross-sectional area of the beam as it traverses the pupil and the size of the pupil itself. It would seem obvious that if the area of the beam is greater than that of the pupil some of the incident light will fall on the iris and only part of the beam will enter the eye. Where the beam has a markedly convergent form, as in the Microlase infrared diode laser, and is aimed at the retina, the beam's cross sectional area at the level of the pupil is likely to be large, hence beam clipping may occur. The same will not be true if the laser is aimed at a point on a plane near the pupil such as the lens capsule.

Woon *et al* make a further point. When an ophthalmoscopic lens of considerable power is being used, say the 90 dioptre lens, the viewing aperture in the pupil is limited (a detailed explanation is given in the paper), so that the laser beam may be suffering iris clipping without the observer being aware of it. It has to be remembered that in addition to possible beam clipping due to the cross sectional area of the beam being bigger than the pupil, clipping will also occur if the beam is not aimed accurately through the pupillary centre, an error which, according to the authors, is easy to make and difficult to avoid.

The practical consequence of these observations is that less power arrives at the retina than predicted by the power settings (and this may be further complicated by inadvertent alterations in spot size, due to a combination of steep vergence and unintentional defocusing, altering the power density at the retina). As the authors point out, the practical remedy is to work with the widest possible pupil but even with this precaution unnoticed beam clipping can still occur owing to the beam not being directed accurately through the pupillary centre.

Apart from this optical form of beam clipping a purely mechanical form is produced by inadvertent interruption of the incident laser beam by the slit-lamp lighting system. The clipping may not appear to affect the aiming beam, so that the observer may be unaware of what is happening and may therefore increase power settings because of the clipping of the main laser beam, thus subjecting the eye to an overdose of laser if the illuminating system is moved slightly and the laser beam unclipped. (It has to be admitted that somewhat the same type of problem can arise from tilting of a tall contact lens or even the interposition of the observer's thumb.) Moseley *et al* describe an ingenious safety device they have developed for the Nanolas laser to inactivate the laser if clipping by the slit-lamp illuminating system occurs, though their device cannot cope with the observer who puts his or her thumb in the way.

REDMOND SMITH

*British Journal of Ophthalmology*, 1991, 75, 386–390

## ORIGINAL ARTICLES

# Iris clipping of a diode laser beam when performing retinal photocoagulation

W H Woon, T J ffytche, A M P Hamilton, J Marshall

**Abstract**

**The Microlase infrared diode laser has recently become available for retinal photocoagulation. It uses a laser beam with a large convergence angle (23°). This gives rise to a laser beam with a relatively large cross section at the subject's pupil. In this study the pupillary area required to view the fundus at the slit-lamp with a 90-dioptre lens is determined. It is found that the pupillary area required to view the fundus is smaller than the cross section of the Microlase laser beam at the pupil. Thus iris clipping of the laser beam can occur even though the surgeon has a clear and bright view of the fundus. Care should be taken to use the Microlase only in the presence of a widely dilated pupil.**

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Accepted for publication 19 February 1991

The Microlase infrared diode laser (Keeler Ltd) has become available for clinical use in retinal photocoagulation. It has been shown to be effective for the treatment of proliferative disease and diabetic exudative retinopathy.[1-3] Surgeons who are using the Microlase for the first time, and who have previous experience with argon lasers, need to adjust to the use of a system with a longer wavelength and a larger convergence angle. Argon laser photocoagulators emit at 488 nm and 514 nm and have a convergence angle of 7° or less. In contrast, the Microlase diode laser emits at approximately 810 nm and has a convergence angle of 23°.[4] The near infrared radiation used by the Microlase is not as well absorbed by melanin as the shorter wavelength used by argon laser photocoagulators.[5] For this reason the Microlase requires higher operating powers than those used by argon lasers.[1-3] The longer wavelength also results in deeper burns, which are grey in colour and less immediately visible than the white burns produced by argon lasers.[1-3]

The surgeon using the Microlase should also be aware that the large convergence angle can lead to greater inadvertent variation in retinal irradiance than a laser system using a small convergence angle. The variation in retinal irradiance can arise from unintentional changes in retinal spot size and iris clipping of the laser beam.[7,8] In most laser systems a larger spot size is achieved by progressively defocusing the treatment beam forward into the choroid. The Microlase achieves a larger spot size by defocusing the treatment beam back into the vitreous. This is performed by the spot size adjuster, which moves the Microlase relative to its base on the slit-lamp. Defocusing of the laser beam could be similarly achieved by keeping the Microlase fixed on its base and moving the slit-lamp away from the patient – that is, by increasing the working distance of the slit-lamp. This must be avoided if the spot size is to remain constant from one burn to the next.

The manufacturers recommend that the working distance of the slit-lamp be held constant by keeping the retina in sharp focus.[4] However, inadvertent variation in the working distance of the slit-lamp can occur even if the retina is held in sharp focus owing to the depth of field of the operator's image and accommodation by the surgeon. Variation in spot size due to inadvertent variation in the working distance can also occur with argon lasers.[7] However, the change in spot size for a given change in working distance is dependent on the convergence angle of the laser used. A small movement of the slit-lamp will cause a greater change in spot size if the convergence angle is large (Fig 1). Thus the spot size at the fundus is more sensitive to changes in the working distance when using the Microlase than when using an argon laser photocoagulator. When using the Microlase it is important to minimise the change in spot size which can occur from pulse to pulse by following the manufacturer's instructions to keep the retina in sharp focus.

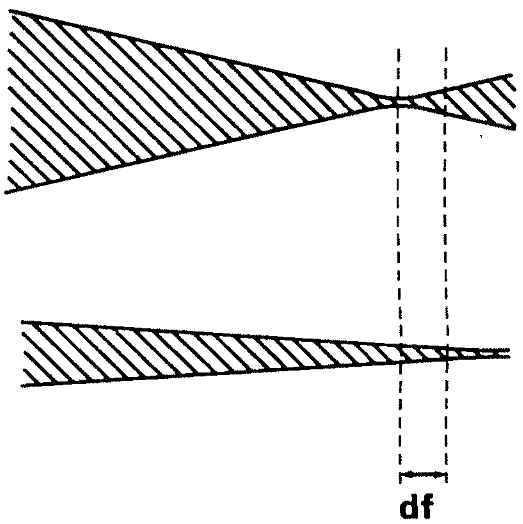


*Figure 1 The laser spot size at the fundus depends on the position of the laser focus relative to the fundus. The top laser beam has a larger convergence angle than the bottom laser beam. There is a correspondingly larger change in spot size over the depth of field* (df) *of the retinal image.*

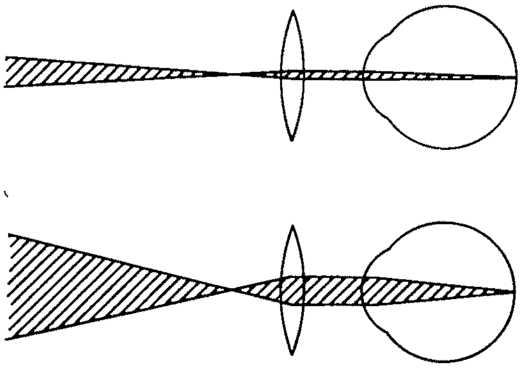


*Figure 2 A laser beam with a large convergence angle produces a wide laser beam at the subject's pupil.*

Iris clipping of the laser beam is not often encountered when using the argon laser photocoagulator owing to the relatively small size of the laser beam.[9] The Microlase is more likely to result in iris clipping because a large convergence angle leads to a large laser beam diameter at the subject's pupil (Fig 2).[8] When using an ophthalmoscopic lens to perform photocoagulation the pupil is not seen, and the operator cannot know whether the fundus is being viewed through the centre of the pupil. In certain circumstances iris clipping can occur without being apparent to the surgeon. For most laser photocoagulators the minimum spot size is achieved by focusing the laser on the fundus. In this situation iris clipping of the laser beam will not produce a similar clipping of the laser spot on the fundus, because the pupil of the eye is an aperture stop and not a field stop.[10] [11] Iris clipping can also occur without changing the surgeon's view of the fundus if the laser beam cross section is larger than the pupillary area required to obtain a clear view of the fundus.

When the fundus is viewed through a slit-lamp, the slit-lamp collects only light passing through a relatively small area of the subject's pupil. This area of the subject's pupil is called the viewing aperture. The viewing apertures are the images of the objectives of the slit-lamp formed by the ophthalmoscopic or contact lens (Fig 3). If the viewing apertures fit into an area smaller than the cross section of the laser beam at the pupil, then it would be possible for the laser beam to be clipped without affecting the view of the fundus.

We have measured the viewing aperture and compared this to the laser beam cross section at the cornea for the Microlase when using a 90-dioptre lens. The results are compared with measurements made for an argon laser photocoagulator. A model eye was then used to test whether iris clipping of the laser beam could occur without affecting the view of the fundus when the Microlase was used with a 90-dioptre lens. The results show that iris clipping may be a significant cause of variation in irradiance at the fundus and therefore the size and intensity of the resulting lesion.

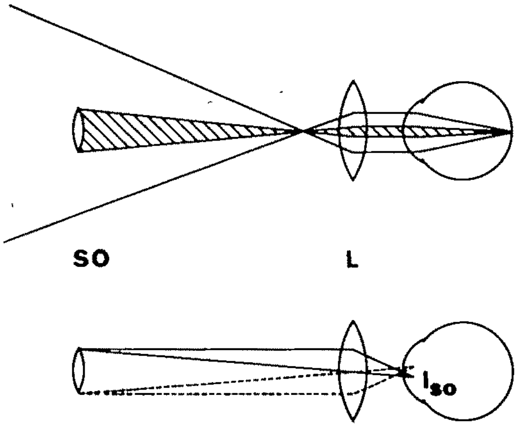


*Figure 3* Top. *The slit-lamp objective* (SO) *collects only light passing through a relatively small area of the subject's pupil. This area is called the viewing aperture.* Bottom. *The viewing apertures are the images of the slit-lamp objective* ($I_{so}$) *formed by the ophthalmoscopic lens* (L).

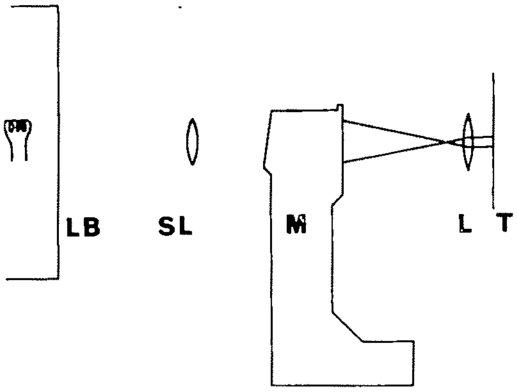


*Figure 4 The viewing apertures may be determined by back illuminating the slit-lamp.* LB: *light box* SL: *slit-lamp.* M: *Microlase.* L: *90-dioptre lens* T: *translucent screen.*

## Materials and methods

The dimensions of the viewing apertures when using a 90-dioptre lens were determined from the principle of reversibility of light rays. The slit-lamp may be back illuminated through the eye pieces to determine the path of light rays from the subject's fundus through the ophthalmoscopic lens and slit-lamp (Fig 4). A Haag-Streit slit-lamp with 10× eyepieces was used, and the viewing apertures were determined for both the 1× and the 1·6× objectives. A Haag-Streit slit-lamp with a Microlase attached was adjusted so that the aiming beam of the Microlase was focused at the working distance of the slit-lamp to produce a minimum spot size of 100 µm.[4] The working distance selector for the Microlase was set to give the short working distance required when using a 90-dioptre lens.[4] A Volk 90-dioptre lens was positioned so that a collimated aiming beam was produced. This procedure would place the 90-dioptre lens in the position it would occupy when being used with an emmetropic

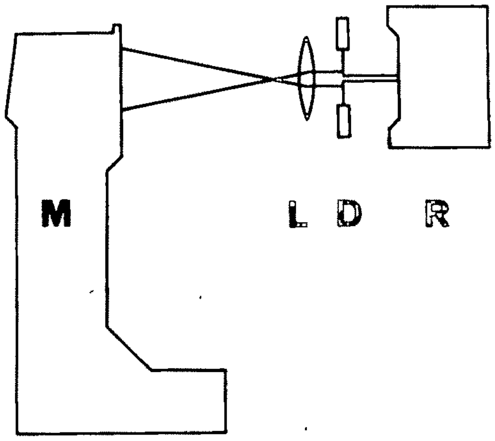


*Figure 5 The beam diameter of the collimated Microlase laser beam may be determined using a variable diaphragm.* M: *Microlase.* L. *90-dioptre lens.* D: *variable diaphragm* R: *radiometer.*

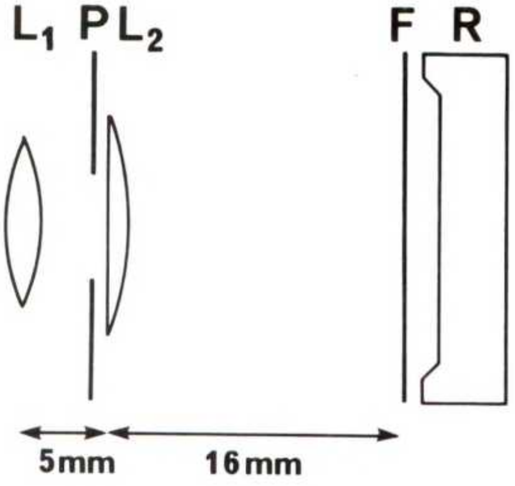


*Figure 6 The model eye used to measure the power reaching the fundus.* $L_1$*: 25 mm lens.* P*: 6 mm pupil.* $L_2$*: 80 mm lens.* F*: filters.* R*: radiometer.*

eye. The slit-lamp was back illuminated with a diffuse extended source (a lightbox). A thin translucent screen with a 1 cm calibration scale was positioned to be coincident with the image of the viewing apertures. The screen was photographed to record the dimensions of the viewing apertures. The approximate dimensions of the aiming beam could be recorded at the same time. The procedure was repeated for a coherent system 900 argon laser photocoagulator and Zeiss slit-lamp. The Zeiss slit-lamp was set at magnification 12 and the laser beam spot size was set at 100 µm.

The beam diameter of the Microlase infrared treatment beam, after being collimated by a 90-dioptre lens, was separately determined (Fig 5). A variable diaphragm was placed in the approximate plane of the pupil, and the diaphragm was centred on the diode beam by means of the inbuilt aiming beam of the Microlase. The power, from the laser, passing through the diaphragm was determined for a range of aperture settings with a radiometer (United Detector Technology Model S370), adjusted for the wavelength of the Microlase.

*Table 1 Dimensions of viewing apertures*

| *Slit-lamp and objective* | *Viewing aperture diameter, mm* | *Separation of centre of viewing apertures, mm* |
|---|---|---|
| Haag-Streit ×1 | 1·2 | 2·5 |
| Haag-Streit ×1·6 | 1·8 | 2·5 |
| Argon ×12 | 1·2 | 2·5 |

To test whether a significant amount of laser energy could be blocked without altering the view of the fundus, a model eye was used incorporating a radiometer in the plane of the fundus (Fig 6). The aperture used to mimic the anatomical pupil was 6 mm in diameter. The radiometer (United Detector Technology Model S370) was used to measure the power of each pulse from the Microlase. A Kodak Wratten 87C filter was employed to block out light with wavelength shorter than 790 nm, and a neutral density filter was used to protect the radiometer. The Haag-Streit slit-lamp had the 1·6× objectives in place and the 90-dioptre lens was positioned in front of the model eye to obtain a view of the centre of the filters. The laser power reaching the radiometer was measured for a fixed laser power setting and for a fixed axial location of the 90-dioptre lens, but with varying degrees of lateral displacement of the lens while retaining the central 6 mm of the radiometer in the field of view through the slit-lamp.

## Results

The viewing apertures and the laser beam cross section recorded when back illuminating the slit-lamp are shown in Figure 7. The dimensions are tabulated in Table 1. All of the energy of the Microlase treatment beam, after it has been collimated by a 90-dioptre lens, passes through a cross section of 5 mm diameter (Fig 8, Table 2). 87% of the energy passes through a cross section of 4 mm diameter.

When using the Microlase with the model eye

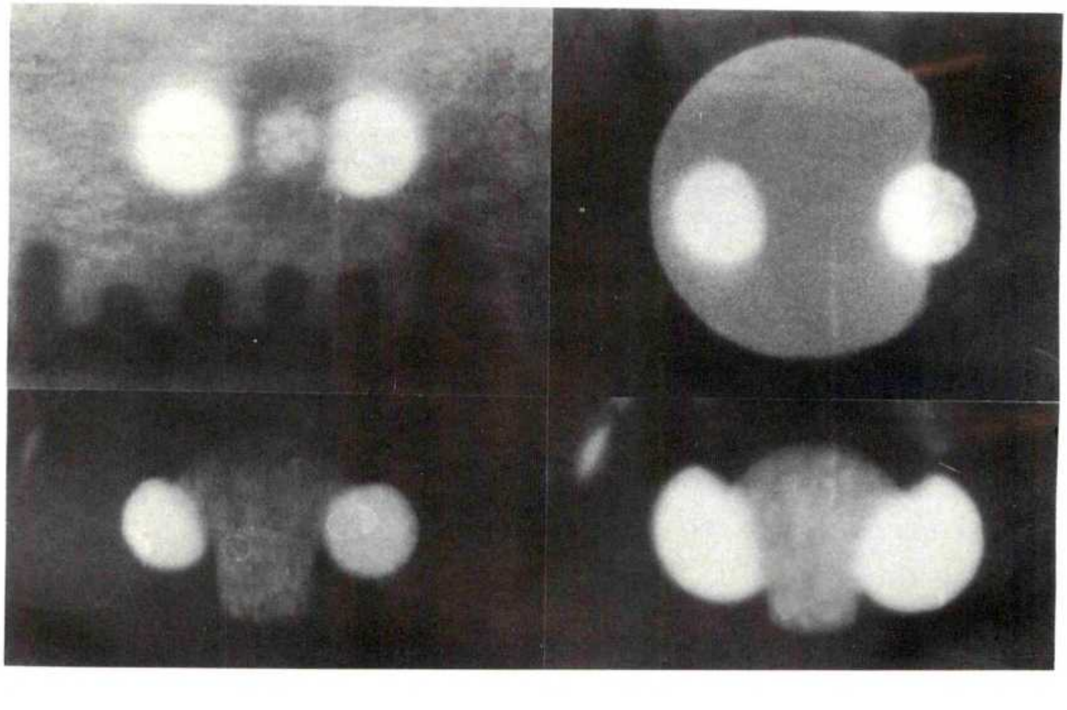


*Figure 7 Photographs of the viewing apertures and laser beam cross section recorded when back illuminating the slit-lamp. The scale has intervals of 1 mm.* Top left: *Viewing aperture of a Zeiss slit-lamp at magnification 12. The argon laser beam lies between the two viewing apertures.* Top right: *Cross section of Microlase aiming beam and viewing apertures of a Haag-Streit slit-lamp with 1× objectives. The viewing apertures lie within the cross section of the Microlase aiming beam.* Bottom left: *Viewing apertures of a Haag-Streit slit-lamp with 1× objectives. The viewing apertures lie either side of the image of the slit-lamp mirror.* Bottom right: *Viewing apertures of a Haag-Streit slit-lamp with 1·6× objectives. The viewing apertures lie either side of the image of the slit-lamp mirror.*

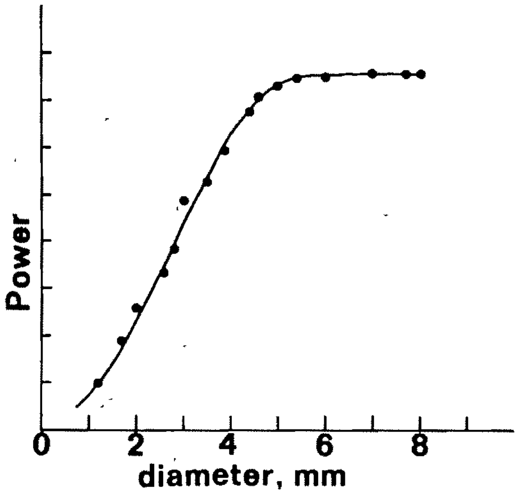
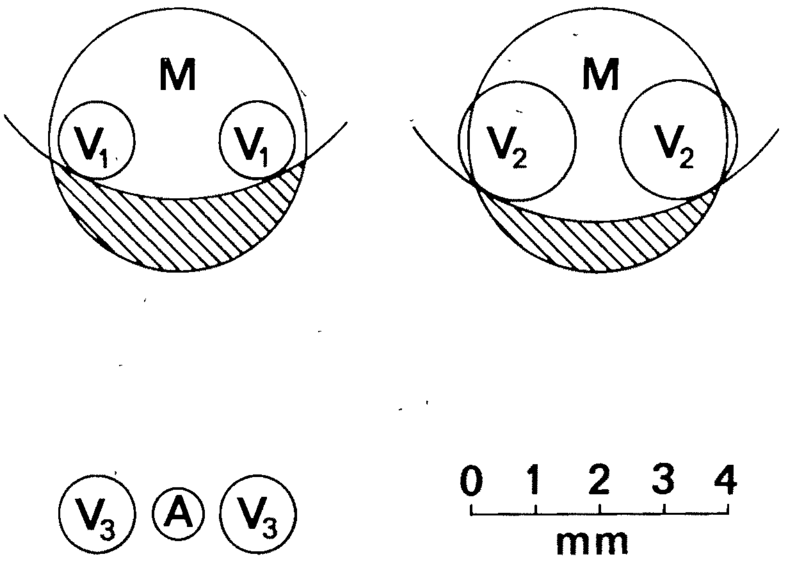


*Figure 8 Plot of laser power passing through the diaphragm versus diaphragm aperture diameter, for the Microlase treatment beam collimated by a 90-dioptre lens.*

*Table 2 The percentage power contained in the central d mm of the Microlase treatment beam collimated by a 90-dioptre lens*

| *Diameter, d mm* | *Power %* |
|---|---|
| 5 | 100 |
| 4 | 87 |
| 3 | 55 |
| 2 | 27 |
| 1 | 8 |

*Figure 9 Viewing apertures and laser beam cross sections at the cornea. The Microlase laser beam may be clipped (hatched area) without clipping the viewing apertures. M: 4 mm laser beam. $V_1$: viewing aperture of Haag-Streit slit-lamp with 1× objective. $V_2$: viewing aperture of Haag-Streit slit-lamp with 1·6× objective. A: argon laser beam. $V_3$: viewing aperture of Zeiss slit-lamp with 12× magnification.*



it was found that the power reaching the fundus in the model eye could vary by 20% by moving the 90-dioptre lens ±5 mm vertically without subjectively altering the view of the fundus. For any given position of the 90-dioptre lens there was no variation of the power reaching the radiometer.

## Discussion

It has been shown, by means of a model eye, that when the Microlase is used with a 90-dioptre lens a 20% variation in the power at the fundus can occur from pulse to pulse. This variation is probably due to iris clipping of the laser beam. When used with a 90-dioptre lens, the Microlase gives rise to a laser beam with a diameter of between 4 and 5 mm. This is larger than the vertical dimensions of the viewing apertures (Fig 9), and thus the laser beam may be clipped by the iris without clipping of the viewing apertures. In comparison, the argon laser beam is smaller than an individual viewing aperture and lies between the two viewing apertures (Fig 9). In this situation it would not be possible to clip the laser beam without clipping the viewing apertures. The argon laser beam may be clipped by partially occluding the viewing apertures while retaining the same field of view, but this is less likely to occur than clipping of the Microlase laser beam.

The viewing apertures and laser beam diameters have been measured without taking into account the effect of refraction by the cornea. However, these results may be compared to the pupil size by using the entrance pupil rather than the anatomical pupil. The imaginary entrance pupil is the image of the anatomical pupil formed by the cornea, and it is 1·15 times the size of the anatomical pupil.[12] The pupil size that is measured without taking into account refraction by the cornea is the size of the entrance pupil. When using a 90-dioptre lens, the surgeon cannot know that the laser beam is passing through the centre of the pupil, and iris clipping of the Microlase laser beam may occur even with the most widely dilated pupil. For a 7 mm entrance pupil 17% of the area of a 4 mm laser beam may be clipped without clipping the viewing apertures when using the 1·6× objectives, and this may rise to 27% for the 1× objectives. The fraction of energy lost due to iris clipping will be less than the fraction of the area of the beam occluded because of the fall in beam energy distribution away from the central axis of the laser beam. However, up to 50% of the laser beam area can be occluded without significantly affecting the surgeon's view other than its becoming progressively dimmer. This is because the viewing apertures themselves are entrance pupils, and partially occluding them would reduce the brightness of the fundal image but not the field of view.

The authors have noted that, when using the Microlase, the lesion size for a given power setting shows more variability than when using argon lasers. It is possible that this is due to clipping of the laser beam by the iris. However, other causes of unintentional variation in retinal irradiance, such as accommodation by the surgeon and the depth of field of the retinal image, may also be important.[7] Uncontrolled variation in the retinal irradiance may be clinically more significant when near infrared lasers are used. A narrow power range for producing a satisfactory lesion in any individual patient has been observed in clinical practice.[2,3] This narrow power range may be more apparent than real. An apparently narrow power range for optimum treatment will be observed if it is difficult to judge the intensity of the burn by its appearance.

When performing retinal photocoagulation with the argon laser, the laser burns are white and are seen immediately in high contrast against the background. Titrating the power level to produce a satisfactory burn is then relatively easy. However, with near infrared radiation the optimum burn is grey, takes time to become visible, and is seen in poor contrast against the background.[1]

These factors, of both visibility and latency, make it relatively difficult to titrate the power of a near infrared laser against the intensity of the burn. In this situation unintentional variation in retinal irradiance would be especially dangerous if the power had been set near the upper level of the range for optimum treatment in the presence of iris clipping.

The principles demonstrated with a 90-dioptre lens also apply to other ophthalmoscopic or contact lenses. The surgeon should obtain as widely dilated a pupil as possible when using the Microlase. However, iris clipping is still possible with the most widely dilated pupil, and may occur because of the difficulty in ensuring that photocoagulation is taking place through the centre of the pupil. In cases where the pupil cannot be dilated widely, the surgeon should consider using a laser with a smaller convergence angle.

*Postscript.* The laser beam characteristics of the Microlase have been modified since this study was performed. However, the convergence angle in the vertical plane remains at 23° and the problems demonstrated in this study remain.

The authors thank Keeler Ltd for supplying a Microlase infrared laser photocoagulator and for helpful discussion concerning its optical system. We are grateful to the Allerton Fund for providing the Allerton research fellowship to support W H Woon.

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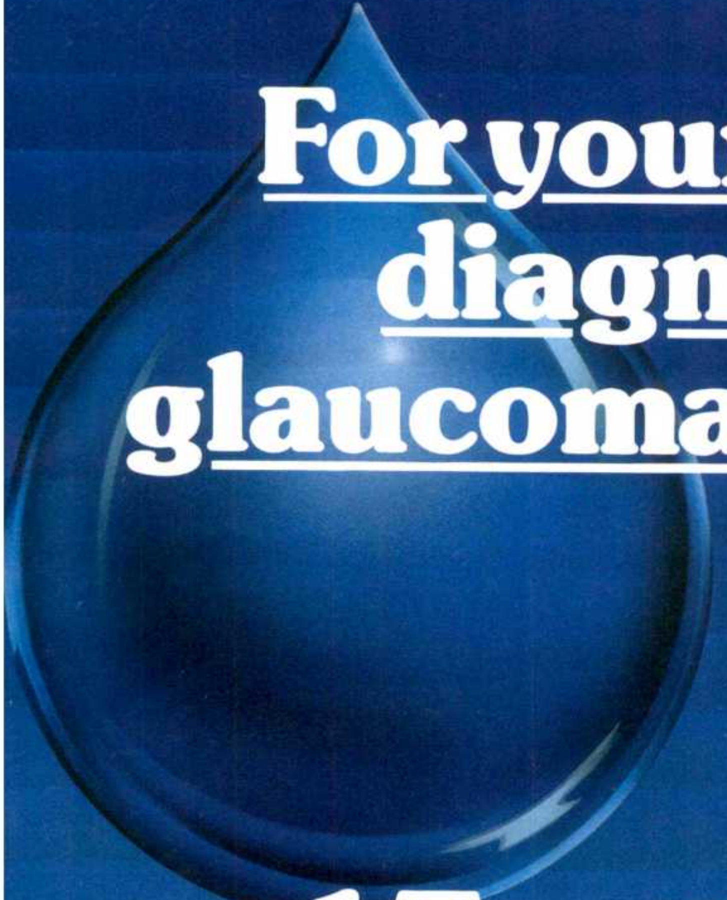

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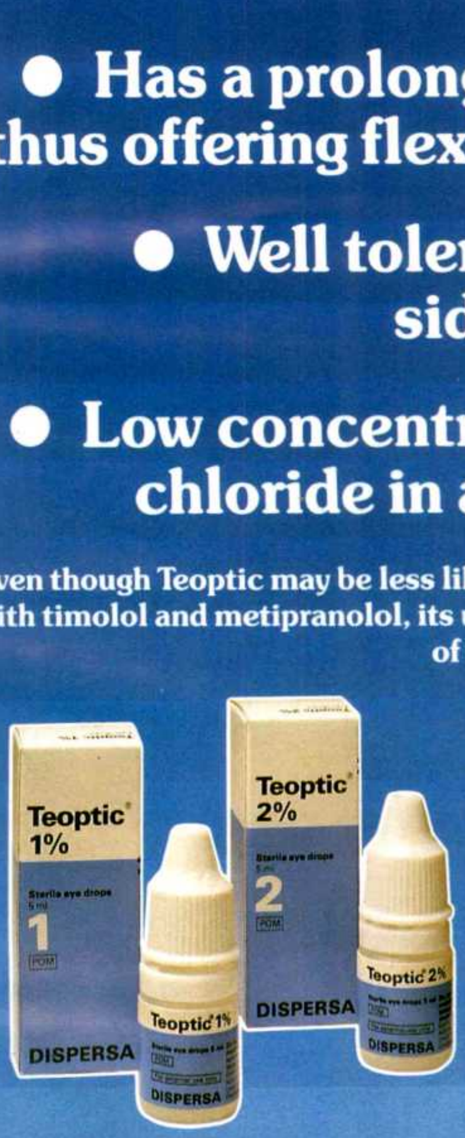

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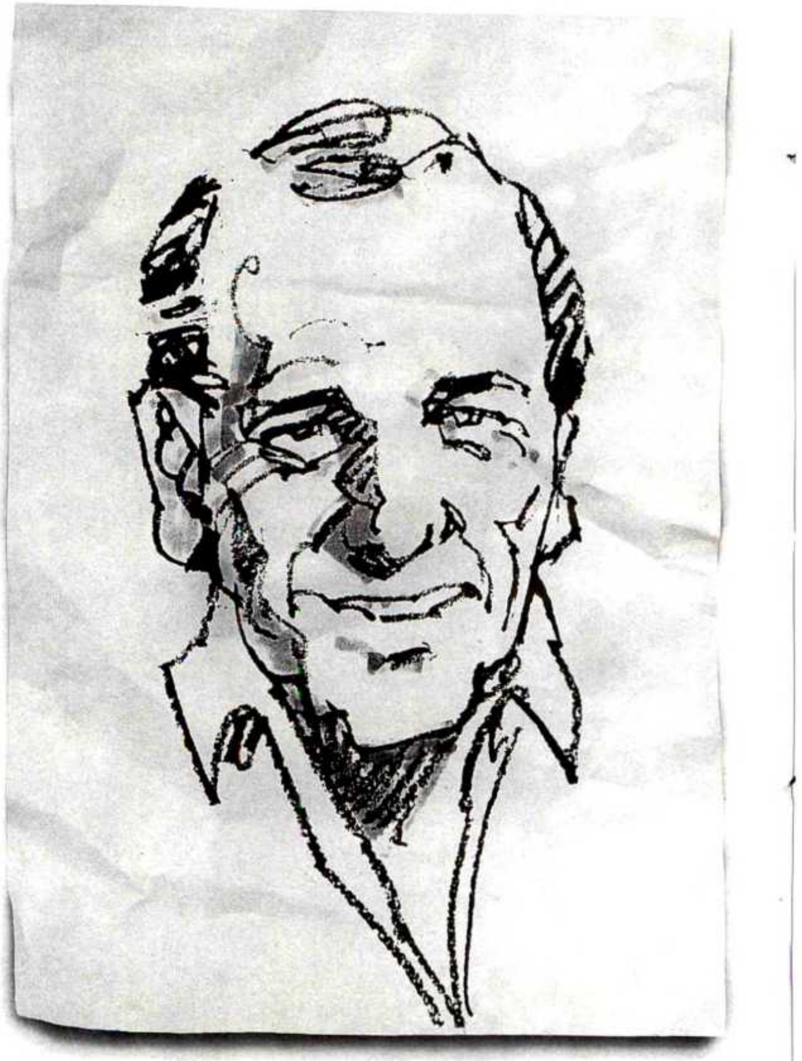

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**PORTON**

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# Ultrastructural pathology of the 'barrier sites' in experimental autoimmune uveitis and experimental autoimmune pinealitis

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## Abstract

**Lewis rats were immunised with retinal S-antigen to induce experimental autoimmune uveitis and experimental autoimmune pinealitis. The blood-retinal and blood-pineal 'barrier sites' were examined by transmission electron microscopy. Inflammatory cell movement through Bruch's membrane involved separation of its constituent layers, cell migration through pores in the membrane, and between retinal pigment epithelial cells without causing significant displacement of the retinal pigment epithelial cell layer. The endothelial cells of retinal and pineal vessels with perivascular infiltrates showed morphological features resembling endothelium of 'high endothelial venules'.**

Experimental autoimmune uveitis (EAU) induced by retinal S-antigen is a T-cell mediated autoimmune disorder and is a good model for chronic intraocular inflammation in humans.[1] S-antigen immunisation also induces an autoimmune pinealitis (EAP) in experimental animals.[2] The administration of an anti-S-antigen monoclonal antibody at the time of immunisation protects the animals from developing EAU[3-5] but not EAP.[4 5] This dissociation of the efferent arc of the immune response was explained by postulating that the monoclonal antibody interacted with the retinal vascular endothelium or the activated T-cells and prevented these cells from breaching the blood-retinal barrier.[4 5] However, in the pineal gland, where the blood-brain barrier does not exist,[6] such a mechanism would not function, and the activated T-cells would have ready access to the S-antigen-containing pinealocytes.

The exact mechanism by which inflammatory cells leave the vascular compartment at sites of inflammation is not clearly understood. Lymphocytes are known to migrate through the vascular endothelium. This process involves a step in which specific receptors on the lymphocyte cell membrane recognise corresponding molecules on the vascular endothelium, resulting in lymphocyte-endothelial adhesion. Such adhesion is an important prerequisite for lymphocyte migration across vascular endothelium.[7] In lymphoid organs and certain chronically inflamed tissues extravasation of lymphocytes occurs through specialised venules known as high endothelial venules. The endothelial cells of these venules are tall and have the specialised function of recruiting circulating lymphocytes and directing them through the vessel wall into the surrounding tissue.[7 8] Antigenic stimulation, of a lymph node for example, is known to induce an increase in its high endothelial vasculature.[9] High endothelial venules have been demonstrated in autoimmune lesions and in immunologically reactive tissue round tumours.[10 11] Whether similar mechanisms directing lymphocyte traffic exist at the blood-retinal and blood-pineal 'barrier sites' in autoimmune uveitis and pinealitis is not known.

The blood-retinal barrier consists of (*a*) Bruch's membrane and retinal pigment epithelium (RPE) layer posteriorly, and (*b*) the retinal vascular endothelium with its tight junctions and lack of fenestrations, anteriorly. The pineal vessels in rats are devoid of tight junctions and are largely fenestrated. We examined these 'barrier sites' in the eyes and pineal glands of Lewis rats with EAU and EAP using transmission electron microscopy.

## Material and methods

Pure bovine S-antigen was prepared by the method of Al-Mahdawi *et al.*[12] Six female Lewis rats, 6 to 8 weeks old, were immunised by a single footpad injection of 50 μg of bovine S-antigen emulsified in complete Freund's adjuvant (total volume of injection was 0·1 ml). The animals also received an intraperitoneal injection of heat inactivated *Bordetella pertussis*, $10^{10}$ cells in 1 ml of phosphate buffered saline. Fourteen to 17 days after immunisation, at the peak of the inflammatory response, the animals were killed and the eyes and pineal glands removed. Four control animals were given adjuvants without S-antigen. The animals were housed and treated in compliance with the British Home Office code of practice for the housing and care of animals used in scientific procedures.

The tissues were fixed in 2·5% glutaraldehyde, embedded in epoxy resin, and processed for transmission electron microscopy (TEM) as described before.[13]

## Results

### POSTERIOR BLOOD RETINAL BARRIER

The choroid was thickened and packed with lymphocytes, monocytes, macrophages, and some polymorphs. In several animals Bruch's membrane was separated into its outer collagenous layer at the choriocapillaris and the inner cuticular layer at the RPE by the invading inflammatory cells (Figs 1A, B). Although Bruch's membrane was separated into its con-

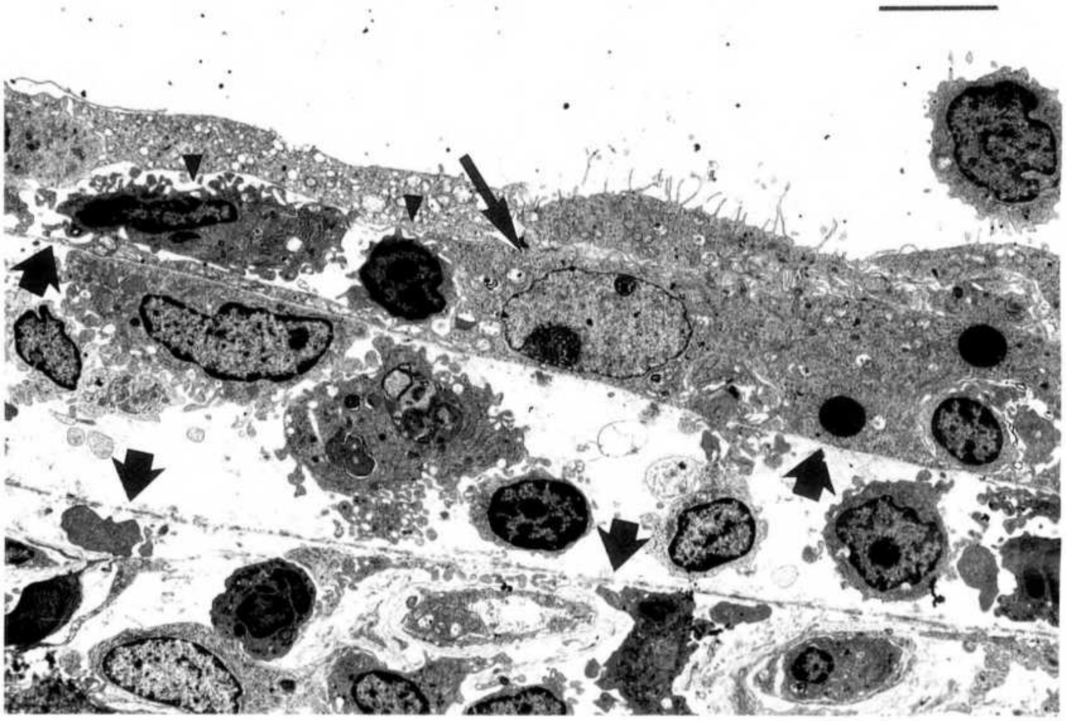

*Figure 1A Separated layers of Bruch's membrane (broad arrows) with inflammatory cells between the layers. RPE cells (long arrow with mononuclear cells (arrow heads) adjacent to it. (Bar=7000 nm.)*

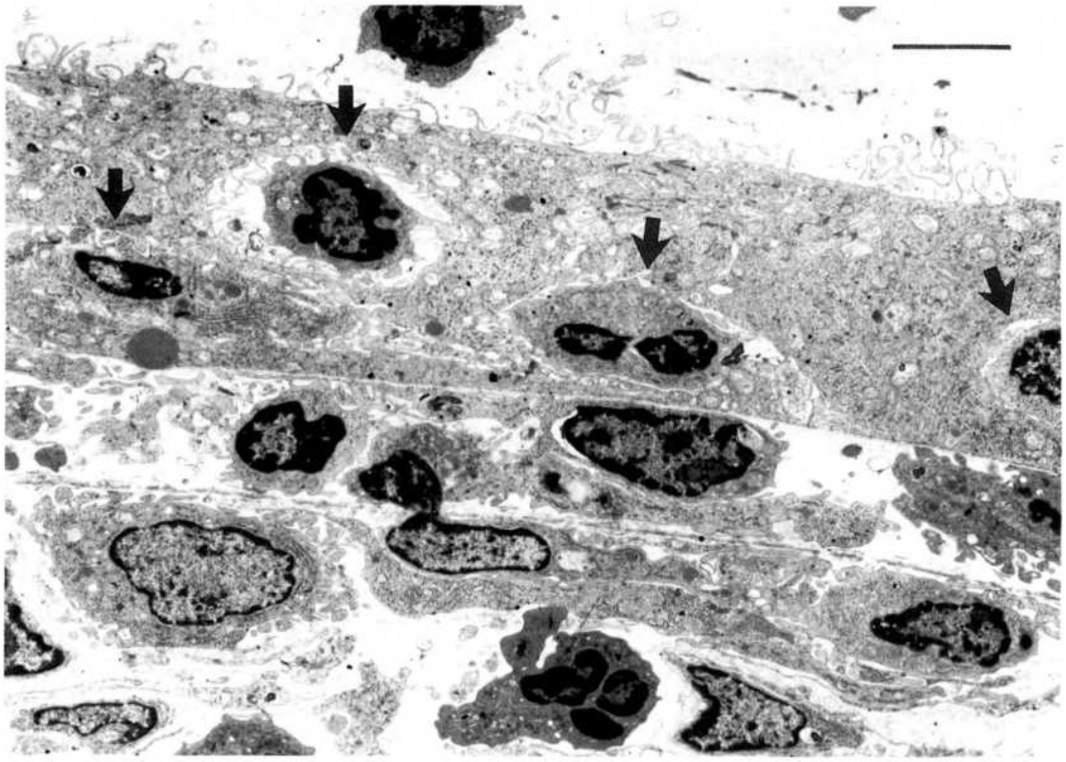

*Figure 1B Inflammatory cells (arrows) lying beneath and between RPE cells. (Bar=4000 nm.)*

stituent components, it remained intact, and inflammatory cells penetrated though pores in the collagenous layers (Fig 1C). The inflammatory cells observed between layers of Bruch's membrane were macrophages, monocytes, lymphocytes, and occasional polymorphs. From Bruch's membrane inflammatory cells passed through the inner cuticular layer and migrated beneath and between the RPE cells (Fig 1B), eventually making their way into the subretinal space (photoreceptor layer). The cells in the subretinal space were predominantly monocytes, lymphocytes, macrophages, and some polymorphs showing evidence of phagocytosis of rod outer segment debris (Fig 1D). In some places these cells formed focal aggregates (Fig 1E). The focal lesions were composed mainly of lymphoid cells with occasional macrophages showing phagosomes. The RPE cells showed stunted or absent processes but remained well preserved and maintained their monolayer distribution even in advanced EAU (Fig 1F). The endothelial cells of the choroid showed a normal flat morphology.

### ANTERIOR BLOOD RETINAL BARRIER

The perivascular infiltrate was predominantly

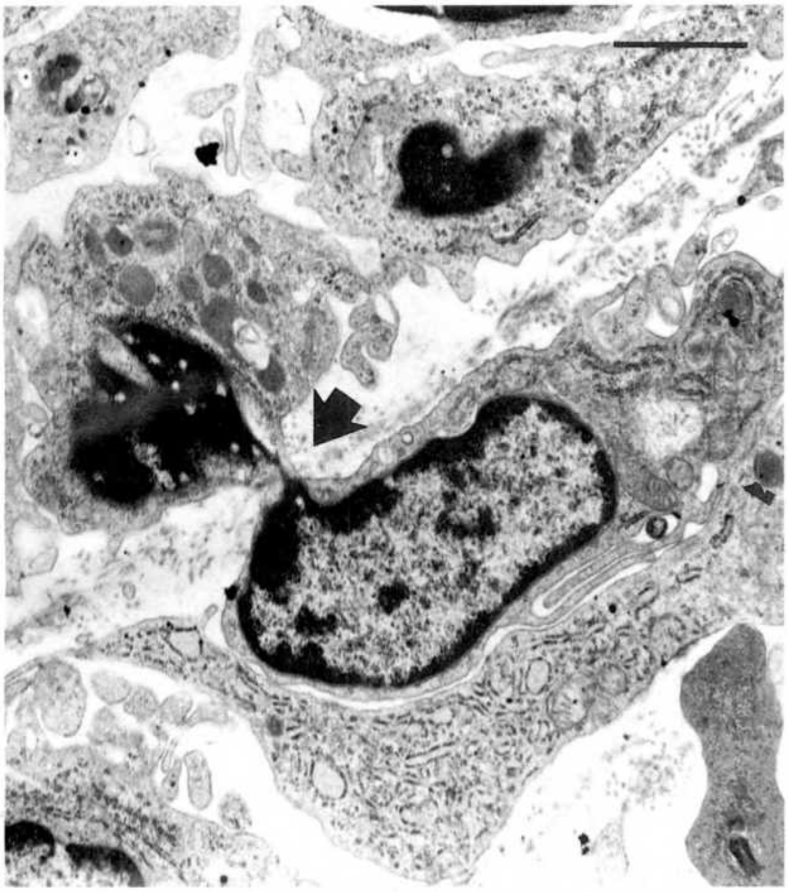

*Figure 1C Mononuclear cell (macrophage) migrating through a pore (arrow) in the separated collagenous layer of Bruch's membrane. (Bar=1300 nm.)*

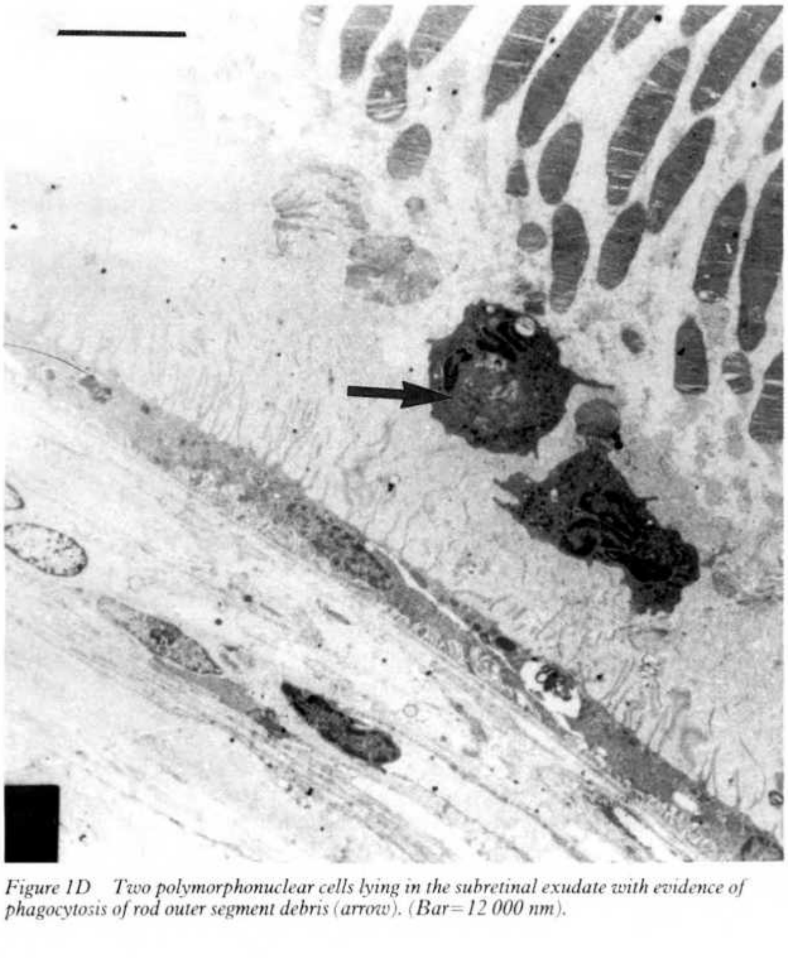

*Figure 1D Two polymorphonuclear cells lying in the subretinal exudate with evidence of phagocytosis of rod outer segment debris (arrow). (Bar=12 000 nm).*

mononuclear showing monocytes, macrophages, and lymphocytes in approximately equal proportions. In addition, as in the choroid, there were some polymorphonuclear cells as well. A large number of inflammatory cells could be seen in the vitreous on one side and extending through the layers of the retina on the other. Inflamed vessels showed tall, plump endothelial cells with irregular pale nuclei containing dense peripheral heterochromatin. The cytoplasm showed prominent rough endoplasmic reticulum, a large number of ribosomes and mitochondria, and occasional large electron dense bodies (Figs 2A, B). The tight junctions of the endothelial cells were found to be intact in all the vessels studied (Fig 2B). At places, platelet thrombi were seen in the retinal vessels. These vessels had flat endothelial cells and showed little evidence of perivascular inflammation.

Control animals showed normal morphology without any evidence of inflammatory cell infiltration in the choroid, subretinal, or perivascular spaces.

### PINEAL BLOOD VESSELS

The inflammatory exudate in the pineal gland was haemorrhagic and exclusively mononuclear, being composed entirely of monocytes, macrophages and lymphocytes (Figs 3A, B). Unlike the retinal exudate there were no polymorphonuclear cells. Almost all lesions were related to blood vessels. Some of the blood vessels were packed with mononuclear cells. The endothelial cells showed similar features to the tall endothelial cells in the retina (Figs 3A, B). All control tissues showed normal morphology.

## Discussion

In the present study we immunised Lewis rats with retinal S-antigen and adjuvant to induce experimental autoimmune uveitis and pinealitis. The animals were killed at the peak of inflammatory response and the eyes and pineal glands studied by transmission electron microscopy. The blood-retinal and blood-pineal 'barrier sites' were studied in detail. The posterior blood retinal barrier site showed splitting of Bruch's membrane and inflammatory cell migration through pores in the split layers. These cells were seen to lie between layers of Bruch's membrane and beneath the RPE cell layer. The RPE retained its monolayer configuration but showed loss of cell processes. Subretinal inflammatory cells were either dispersed in the subretinal fluid or formed focal granulomatous lesions. These cells were monocytes, macrophages, lymphocytes, and occasional polymorphs. The anterior blood retinal barrier – that is, the retinal blood vessels – showed perivascular infiltration with monocytes, macrophages, lymphoyctes, and polymorphs. The endothelium of the inflamed vessels showed morphological features resembling high endothelial venules. Pineal inflammation was manifest as multiple foci of perivasculitis, particularly in the subcapsular region and at the junction of the pineal stalk with the body of the gland. The endothelium of inflamed pineal vessels also showed morpho-

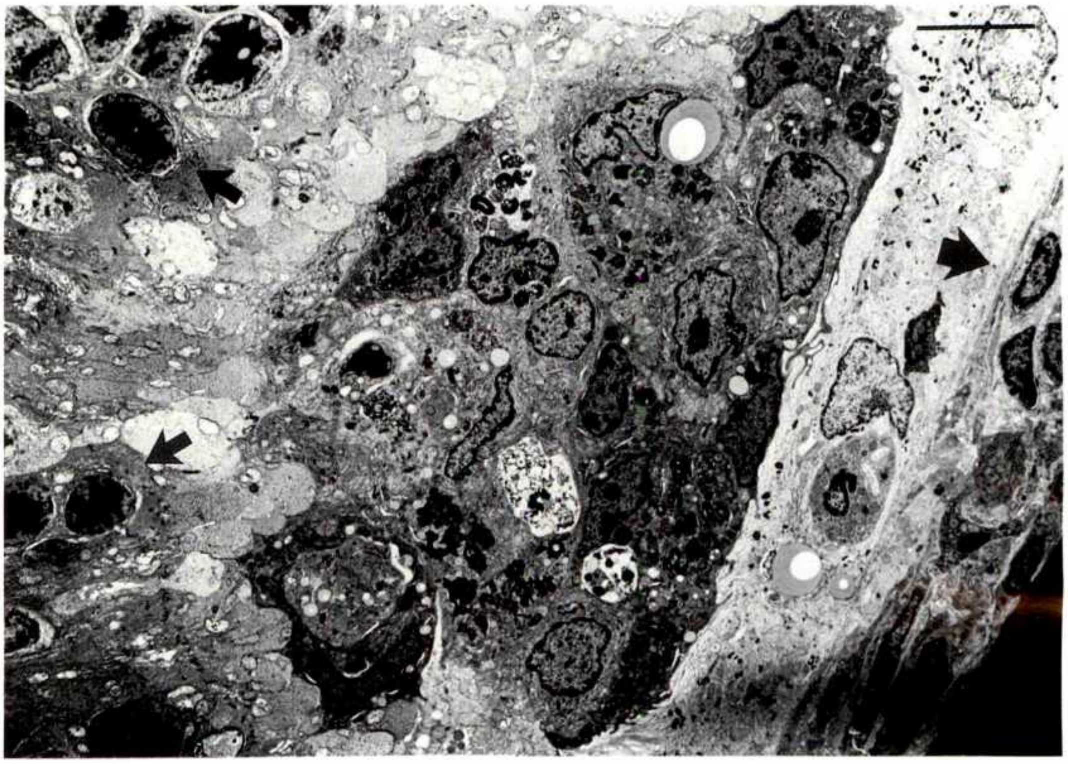

*Figure 1E Focal lesion between Bruch's membrane (large arrow, right) and photoreceptor nuclei (small arrows, left). (Bar= 7000 nm.)*

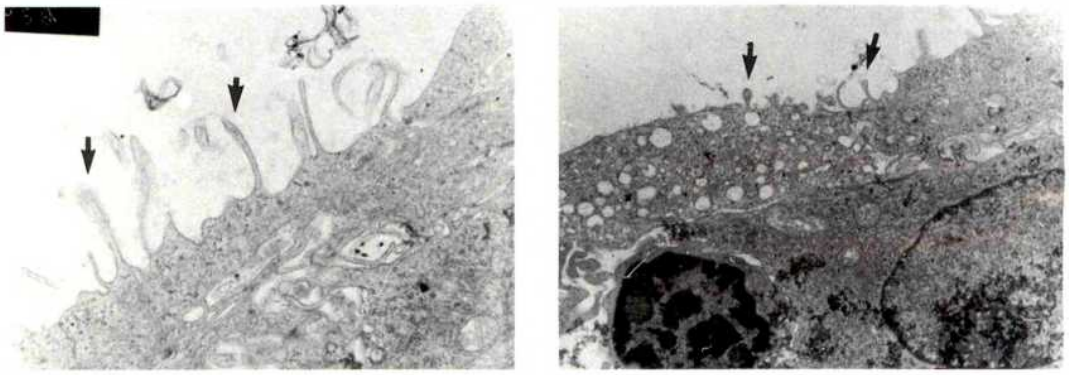

*Figure 1F Stunted and disorganised processes of RPE cells (arrows). (Bar= 3000 nm).*

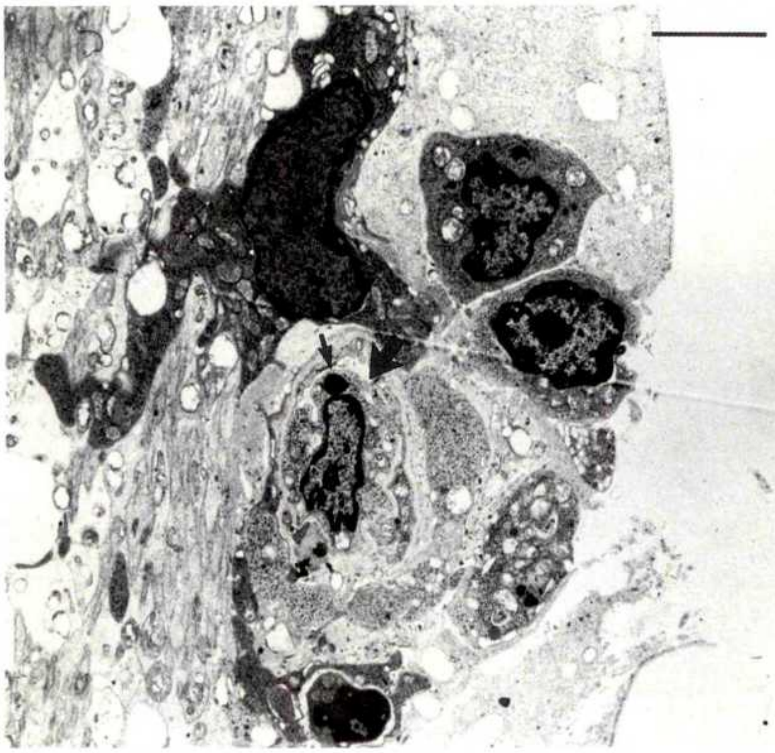

*Figure 2A Retinal vasculitis, tall endothelial cell occupying most of the vessel lumen (large arrow). Note the large dense cytoplasmic body (small arrow) and irregular nucleus. (Bar=4000 nm.)*

logical features resembling high endothelial venules. The inflammatory infiltrate round pineal blood vessels was haemorrhagic and composed of monocytes, macrophages, and lymphocytes. There were no polymorphs at this site.

Previous studies on the ultrastructural changes in EAU have focused on the posterior blood-retinal barrier. Although perivasculitis is an early feature of EAU in rats, changes occurring in the vascular endothelium have not been described in detail. Faure and associates[14] studied in guinea pigs the electron microscopic features of uveitis induced by immunisation with retinal extracts. They observed the presence of lymphocytes, monocytes, macrophages, and polymorphs in the choroid. They also reported lymphoid nodules resembling Dalen-Fuchs nodules of sympathetic ophthalmia. These nodules were composed of immunoblasts and showed evidence of mitosis. The presence of blast cells and mitotic figures led them to postulate that a local proliferation of lymphoid cells ocurred in the eye during the course of EAU induced by retinal extracts. Forrester and associates[13] also studied electron microscopic features of EAU in guinea pigs. They used purified S-antigen in their model and reported an early appearance of isolated macrophages among the disrupting rod

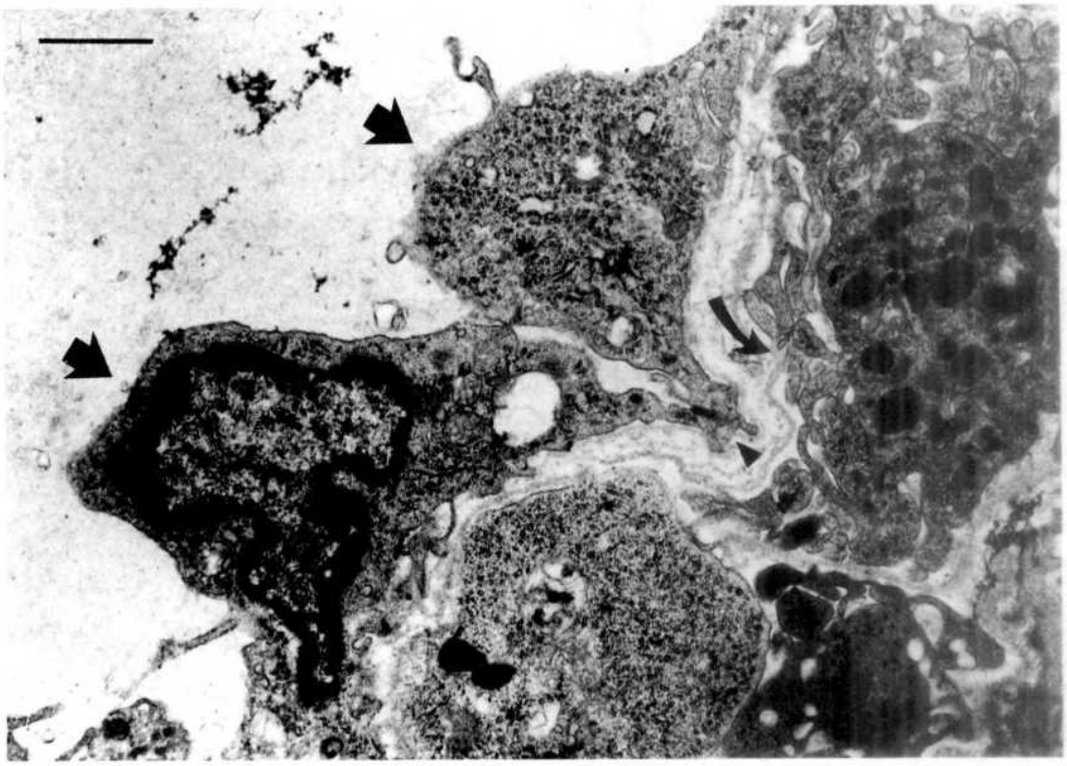

Figure 2B Two tall endothelial cells in a retinal vessel (large arrows). Note the irregular pale nucleus and abundant rough endoplasmic reticulum. The cell junction is intact (arrow head). A macrophage (curved arrow) lies adjacent to the basement membrane. (Bar=800 nm.)

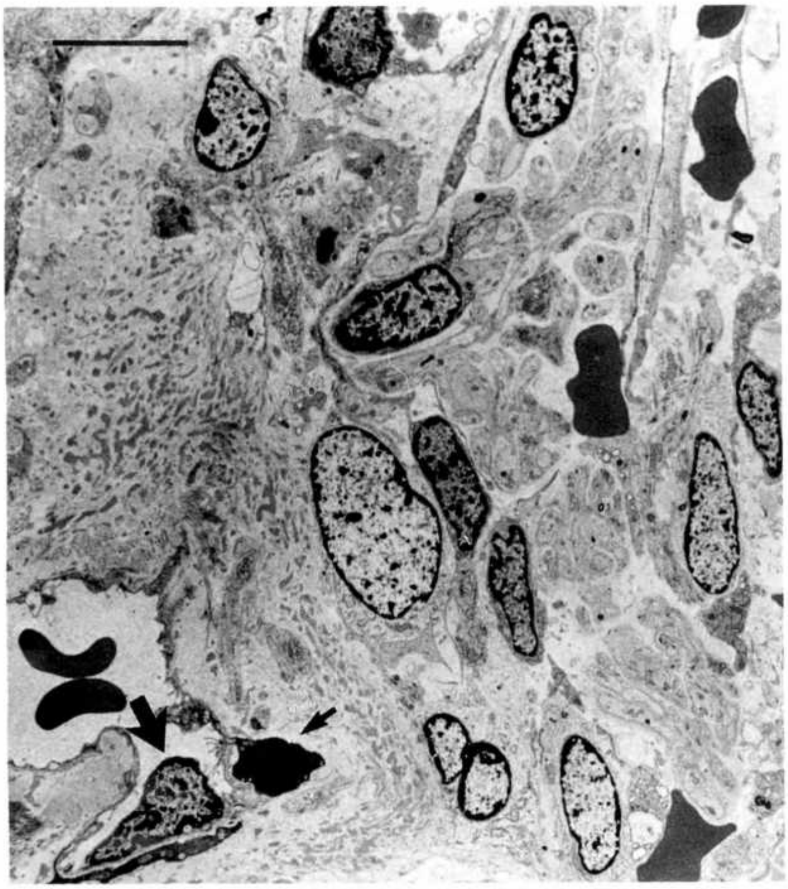

Figure 3A Pinealitis, a tall endothelial cell (large arrow, left) with a mononuclear cell outside the vessel wall (small arrow). Surrounding haemorrhagic, mononuclear exudate. (Bar=10 000 nm.)

outer segments. This was followed by a massive choroidal infiltration with mononuclear cells including macrophages with abundant cytoplasm and phagosomes. Polymorphonuclear cells were also present in the infiltrate.

Both these studies differed significantly from the present study because the guinea pig retina, unlike the rat (and human) retina, is devoid of blood vessels. Changes occurring in and around retinal blood vessels could therefore not be studied.

De Kozak *et al*[15] studied the electron microscopic features of a hyperacute form of EAU in Lewis rats. They too used whole retinal extracts obtained from guinea pig or rat eyes to induce EAU. They reported the invasion of capillary walls by polymorphonuclear cells but have not commented on the state of the vascular endothelium. None of the previous studies have documented the ultrastructural features of the associated pineal inflammation or made any attempt to explain the mechanism of inflammatory cell migration across the blood-retinal barrier.

Lymphocyte migration is an important prerequisite for the proliferation, differentiation, and selective distribution of antigen specific cells. The migration of lymphocytes through the vascular endothelium involves specific lymphocyte-endothelium adhesion mechanisms that direct lymphocytes from the blood stream into lymphoid organs or inflamed tissues. In lymphoid organs migration occurs through a specialised vascular endothelium of postcapillary venules, called high endothelial venules (HEVs).[7-9] Lymphocytes have been shown to bind selectively to the endothelium of HEVs via specific receptors known as lymphocyte homing receptors. Lymphocyte homing receptors recognise and specifically bind to corresponding receptors on the endothelium of HEVs. These endothelial adhesion receptors are known as 'vascular addressins'.[7] HEVs are normally found in all secondary lymphoid tissues except the spleen. However, HEV-like structures are known to develop in chronic inflammatory conditions, including autoimmune lesions, and in cell mediated immune reactions in the skin

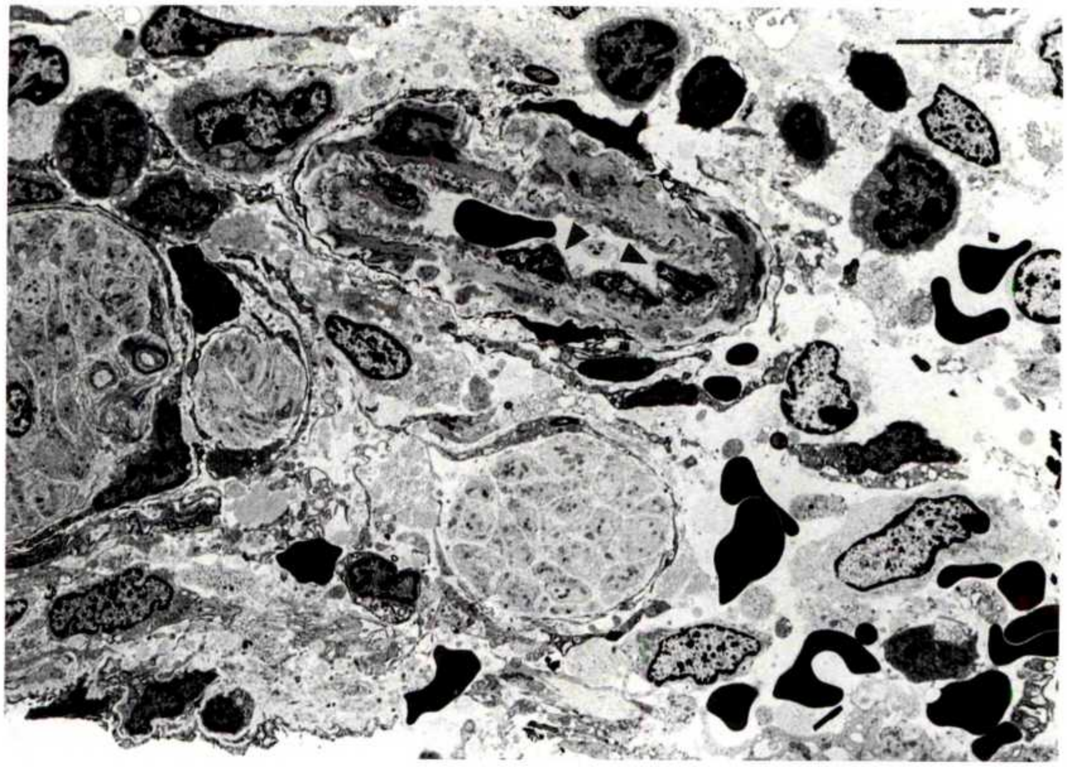

*Figure 3B Pineal vasculitis, several tall endothelial cells (arrow heads, centre) with a perivascular haemorrhagic mononuclear exudate. (Bar=10 000 nm.)*

and synovial membrane.[10] The endothelium of HEVs is cylindrical or cuboidal in shape. They contain electron dense organelles, numerous free and clustered ribosomes, and abundant rough endoplasmic reticulum. These cells also show occasional large dense bodies in the cytoplasm, unlike other endothelial cells. The nuclei are large, pale, and irregular. The chromatin is loose centrally and condensed at the periphery.[8 9]

In the present study all retinal blood vessels with perivascular infiltrates showed altered endothelial cells with some morphological features similar to the endothelial cells of HEVs. The endothelial cells were plump, cuboidal in shape, with prominent rough endoplasmic reticulum and a large number of ribosomes and mitochondria. Some of them also showed large electron dense bodies in the cytoplasm. These changes may be related to the recruitment and migration of lymphocytes across the blood retinal barrier.

How inflammatory cells cross the blood-retinal barrier is unclear. The obvious path, as suggested by Duijvestijn and Hamann,[7] would be through the endothelial cell junctions. We did not observe any breach in the junctions of endothelial cells in any of the HEV-like vessels studied. On the contrary, the junctions between high endothelial cells seemed to be well preserved, even though inflammatory cells were seen immediately outside the vessel wall. It is possible that in retinal vessels the cell junctions temporarily open to permit lymphocyte exodus and rapidly re-form after the cell has passed through. Migration of lymphocytes through the endothelial cell (transcytosis) may be an alternative mechanism.

Although the choroid showed a considerable amount of inflammatory cell infiltrate, the endothelial cells of choroidal vessels did not show any of the changes observed in the retinal vascular endothelium. This would suggest that vascular endothelial cell participation in the inflammatory process at this site is different from that in the retinal vessels.

In previous studies[14 15] on the ultrastructural pathology of EAU it is suggested that the migration of inflammatory cells from choroid to the subretinal space occurs through breaks or defects in the RPE/Bruch's membrane layer. This does not appear to be essential, as illustrated in this study, where inflammatory cells were shown to migrate through pores in the Bruch's membrane which was separated into two layers with inflammatory cells lying in between. From here cells migrated to lie beneath and between RPE cells leaving the RPE layer essentially intact. Subretinal focal lesions were observed on intact Bruch's membrane indicating that the migration of cells from the choroid to this site is more complex than a mere influx of cells through a breach in the RPE/Bruch's membrane layer. The use of retinal extracts rather than S-antigen in the previous studies may have induced a more severe form of EAU with destruction of the RPE/Bruch's membrane layer.

The pineal inflammatory response was essentially a perivasculitis involving predominantly vessels located in the subcapsular region and at the junction of the pineal stalk with the body of the gland. Like retinal vessels, the pineal vascular endothelium showed features of increased metabolic activity and a morphological resemblance to HEVs. The pineal inflammatory exudate differed from the retinal exudate in two respects. There were a large number of red blood cells and a striking lack of polymorphonuclear cells in the pineal exudate. The presence of red blood cells in the pineal perivascular exudate would indicate increased fragility and ready extravasation at this site. In spite of this the absence of polymorphonuclear cells from the exudate would suggest that specific mechanisms which are involved in the recruitment of these cells operate in the retina but not in the pineal gland. As in retinal vessels, endothelial cell junctions of pineal vessels remained intact, even though the cell morphology was considerably altered. However, at this site inflammatory cell migration through fenestrations in the endothelial lining was more likely.

The differences in the vascular endothelial response between the pineal and retinal vessels on the one hand and the choroidal vessels on the other, and the differences in the composition of the inflammatory exudate in the eye and pineal gland during the course of an inflammation induced by a common antigen, S-antigen, would suggest that more than one mechanism is involved in the recruitment and migration of antigen specific lymphocytes and that these mechanisms are, to some extent, specific to the tissue involved. Surface receptors (vascular addressins) expressed by the endothelial cells of inflamed vessels, which interact with lymphocyte homing receptors, may have an important role in determining the nature of inflammatory exudate in the eye and pineal gland. Differences in the inflammatory cell infiltrate between eye and pineal gland may be due to expression of different receptors (addressins) at these sites. If it can be demonstrated that specific surface receptors (vascular addressins) are in fact expressed on the endothelium of retinal and pineal vessels in EAU and EAP, it may prove to be an important mechanism in the recruitment of activated antigen specific lymphocytes in these autoimmune disorders.

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# Review of fluorescein angiograms performed in one year

W N Wykes, S J Livesey

**Abstract**

**In this study 374 consecutive fundus fluorescein angiograms (FFAs) were performed on 330 patients. Of these, 165 (50%) were investigated for age related maculopathy. In only 12% did this investigation lead to an alteration in treatment. The remaining 50% of angiograms were requested for diabetic patients (15%), retinal vein occlusion (5%), tumours (6%), and various other disorders. In the diabetic patients treatment could have proceeded without FFA in 24% of patients who underwent it. Missed diagnoses corrected by angiography and areas where unnecessary angiograms were performed were identified. One interesting subgroup of eight patients with unexplained loss of central vision was identified. Careful clinical examination had failed to reveal any abnormality. FFAs were of no diagnostic value in these patients.**

Fluorescein angiography has been available as an aid in the diagnosis and assessment of many ophthalmic conditions since its introduction by Novotny and Alvis in 1961.[1] Previous studies have suggested the main area in which it is helpful.[2-6] These are: macular disease; retinal vascular disease; the optic disc; ocular tumours. However, few papers have tried to quantify its value.[7-9]

In this study we assess the reason for performing the test and its usefulness in the management of the patient concerned.

## Material and method

All the fundus fluroescein angiograms (FFAs) performed in 1986 in two centres, the University Hospital of Wales, Cardiff (catchment: 542 000) and St Woolos Hospital, Newport, Gwent (catchment: 440 000) were examined to ascertain the reasons for requesting the test, the distribution of conditions investigated, and the outcome – that is, whether the FFA altered management and if so what the final visual outcome was.

Three hundred and seventy four FFAs on 330 patients are included in the study. Thirty four patients underwent more than one FFA, totalling 78 between them (Table 1).

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*Table 1 Fluorescein angiograms performed*

| *Hospital* | *FFA performed* | *Notes not found* | *FFA in study* | *Patients in study* | *Patients with repeat FFA* |
|---|---|---|---|---|---|
| UHW, Cardiff | 279 | 44 | 235 | 211 | 22 |
| St Woolos, Newport | 147 | 8 | 139 | 119 | 12 |
| Total | 426 | 52 | 374 | 330 | 34 |

*Table 2 Indication for FFA*

| | *UHW* | *St Woolos* | *Total* |
|---|---|---|---|
| Maculopathies: | 111 | 54 | 165 |
| senile macular degeneration | 1 | 5 | 6 |
| central serous retinopathy | 18 | 4 | 22 |
| cystoid macular oedema | 1 | 4 | 5 |
| Foerster-Fuchs maculopathy | 1 | 2 | 3 |
| preretinal gliosis | 5 | 1 | 6 |
| retinal pigment epithelial detachment | 0 | 1 | 1 |
| choroiditis | 3 | 1 | 4 |
| circinate retinopathy | 6 | 1 | 7 |
| aneurysm | 3 | 1 | 4 |
| hereditary maculopathy | 5 | 3 | 8 |
| unexplained poor vision | | | |
| Retinal vascular disease: | 27 | 23 | 50 |
| diabetes | 10 | 8 | 18 |
| venous occlusion | 0 | 1 | 1 |
| periphlebitis | 1 | 0 | 1 |
| hypertension | | | |
| Optic disc: | 4 | 3 | 7 |
| papilloedema | 1 | 0 | 1 |
| drusen | | | |
| Ocular tumours: | 13 | 7 | 20 |
| malignant melanoma | 1 | 0 | 1 |
| metastases | 211 | 119 | 330 |
| Total: | | | |

In all cases 20% sodium fluorescein was used intravenously. No serious side effects were reported.

## Results

### INDICATION FOR FFA

Maculopathy was, as expected, the commonest indication, particularly to ascertain the presence and location of disciform maculopathy. Diabetic retinopathy was also a fairly common indication. Table 2 lists the indications: 231 patients were investigated for maculopathy other than diabetic maculopathy, of whom 165 had clinical evidence of senile macular degeneration, 58 were thought to have other macular pathology, and eight were thought to have normal fundi, with unexplained poor visual acuity.

Fifty patients were diabetic, and the remaining 50 were investigated for malignant melanoma, venous occlusion, papilloedema, periphlebitis, disc drusen, and choroidal metastases.

Of the 34 patients who underwent more than one FFA 30 had a disciform macular degeneration. Of these, 26 had two FFAs, three had three FFAs and one had eight FFAs. Of the remaining four patients one had a malignant melanoma, treated by laser (three FFAs), one had dry senile maculopathy (two FFAs), one had choroiditis (two FFAs), and one had a venous occlusion (two FFAs).

### RESULTS OF FFAS

*Maculopathy.* FFAs were performed on 165 patients with the clinical diagnosis of age related macular degeneration. Seventy (42%) were

*Table 3 Macular degeneration*

| | |
|---|---|
| Maculopathy: | |
| 70 dry maculopathy | |
| 18 misdiagnosed | |
| 77 disciform maculopathy | 57 subfoveal, no treatment |
| | 20 treatable, laser |
| Total 165 | |

shown to have dry maculopathy, 18 (11%) had been misdiagnosed, and 77 (47%) had subretinal neovascularisation, of whom 57 had untreatable subfoveal neovascularisation while the other 20 (12%) received laser treatment (Table 3).

In the treated group the average initial vision was 6/24 and the final vision 6/36. Three patients were improved when last seen, two remained static, and the rest deteriorated. Follow-up time ranged from one to 18 months. One patient maintained a visual acuity of 6/18 for 15 months before deteriorating, but the rest deteriorated within three months of treatment.

Table 4 shows the other maculopathies, excluding diabetic maculopathy. One patient thought to have cystoid macular oedema was found to have central serous retinopathy, and another had a microaneurysm. Three cases of circinate retinopathy were examined, one due to aneurysms and treated with laser, and one with a leaking site close to the macula for which treatment with laser was offered but was declined.

One case of choroiditis had changes consistent with presumed ocular histoplasmosis syndrome; one patient with suspected hereditary macular degeneration was shown to have a gross pigment defect centrally in both eyes.

Eight patients with unexplained poor visual acuity underwent fluorescein angiography to eliminate any maculopathy, but all were found to be normal, suggesting that FFA is unhelpful in the absence of clinically observable changes.

*Diabetic retinopathy.* The reasons for investigation in the 50 diabetic patients included in the study are shown in Table 5.

Following angiography 10 of the 25 patients with maculopathy received laser treatment. All the patients with circinate retinopathy received laser treatment, but only three showed leakage of fluorescein. Six of the nine patients with possible preproliferative disease showed sufficient changes to warrant laser treatment. Disc new vessels were confirmed in five of six patients, and they received a laser panretinal ablation to the affected eye. However, in two of these patients the new vessels were recorded as obvious clinically and were readily identifiable on colour fundus photograph alone, so that, as with the 10 cases of circinate retinopathy, FFA did not influence the management of the patient.

*Table 4 Outcome of other maculopathies*

| *Clinical diagnosis* | *No* | *Confirmed* | *Not confirmed* |
|---|---|---|---|
| CMO | 22 | 12 | 10 |
| CSR | 6 | 2 | 4 |
| RPE detachment | 6 | 3 | 3 |
| Foerster-Fuchs | 5 | 1 | 4 |
| Isolated aneurysm | 5 | 3 | 2 |
| Preretinal gliosis | 3 | 2 | 1 |
| Circinate retinopathy | 3 | 3 | – |
| RPE defect | 3 | 3 | – |
| POHS | 1 | 1 | – |
| Hereditary macular degeneration | 1 | 1 | – |

CMO=cystoid macular oedema. CSR=central serous retinopathy RPE=retinal pigment epithelium. POHS=presumed ocular histoplasmosis syndrome.

*Table 5 Diabetic retinopathy*

| *Clinical diagnosis* | *No* | *Confirmed* | *Revised* | *Unhelpful* | *Laser* |
|---|---|---|---|---|---|
| Maculopathy | 25 | 10 | – | 15 | 10 |
| Circinate | 10 | 3 | – | 7 | 10 |
| Preproliferative changes | 9 | 6 | 2 | 1 | 6 |
| Disc new vessels | 6 | 5 | 1 | – | 5 |

*Vascular occlusion.* Eighteen patients with venous occlusion underwent FFA. Two of these were for retinal vein occlusion with possible capillary closure, neither of which required laser treatment; 11 were for branch vein occlusion, some with secondary maculopathy; six received laser treatment; three patients with branch vein occlusions were misdiagnosed as disciform macular degeneration, two of whom received laser treatment; two patients with collaterals at the optic disc underwent FFA to ensure that these were not new vessels.

One patient with Crohn's disease was noted to have perivenous sheathing. An FFA did not show any evidence of periphlebitis.

*Tumour.* Twenty patients with pigmented fundus lesions were investigated. Twelve were shown to have choroidal naevi, one had a serous retinal detachment with no definite underlying mass, and seven had appearances typical of malignant melanoma. Three of these patients underwent enucleation, with subsequent confirmation of the diagnosis. Two were managed conservatively (by observation), one received radiotherapy, and one had a small malignant melanoma which was treated with laser. This patient has required several further applications of the laser.

In one patient a choroidal metastasis was confirmed.

*Optic disc.* Seven patients underwent FFA for suspected papilloedema. Two were confirmed and three appeared completely normal. One, with reduced vision, had a genuinely swollen left disc and a diagnosis of papillitis was made. One with normal vision and a unilateral swollen disc was shown on FFA to have a juxtapapillary lesion, by which time the visual acuity had fallen. A diagnosis of juxtapapillary choroiditis was made, and the patient was started on systemic steroids, with full recovery of visual acuity.

Three patients were thought to have disc drusen, which were confirmed in two of them.

*Misdiagnosed conditions.* Eighteen patients with an original diagnosis of disciform macular degeneration were found after FFA to have the following: pigment epithelial detachments (five patients), pigmentary changes associated with preretinal gliosis (five patients), small branch retinal vein occlusions (six patients), microaneurysm (one patient), and naevus (one patient).

## Discussion

This survey shows that fluorescein angiography is used in these units mainly as expected, with the single largest indication being macular degeneration. It must be remembered that the spectrum of disease shown does not represent that seen in the clinic as many cases can be treated on clinical grounds alone.

Over 40% patients investigated for possible disciform maculopathy were found to have dry changes only, and it should be possible by careful clinical assessment to reduce this number. Part of the reason for this was that contrary to unit policy some of the FFAs had been requested by doctors other than consultants and senior registrars. Review of the visual acuity and colour fundus photographs suggested that the unnecessary FFAs had often been requested by more junior members of staff, and it is recommended that FFAs should only be requested by more experienced ophthalmologists.

As age related maculopathy was the commonest reason for requesting an FFA, the clinical course and final visual outcome were examined in a little more detail to give some idea of the 'usefulness' of the investigation in this condition. The results of treatment of the patients with apparently treatable disciform maculopathy were disappointing.

It has been suggested that patients with age related maculopathy should be seen urgently, particularly if the history of visual disturbance is short and the visual acuity is good.[10] Unfortunately this information is not always available on referral letters, and this raises the question whether all cases referred with possible macular degeneration should be seen urgently or routinely in units where the routine waiting time for new appointments may be several months. This paper did not set out to answer that question, but it does show that when disciform lesions which do not involve the fovea on FFA are treated the visual results are poor. Those patients with maculopathy investigated by fluorescein angiography are a small percentage of those seen in the clinic, as many patients are obviously not treatable on clinical grounds. Of 163 patients *investigated* 20 received treatment, five of whom maintained or improved their visual acuity and one of whom improved for more than three months. Is it justifiable to displace outpatient appointments for patients with known treatable conditions such as cataract for such a low yield in terms of improved visual acuity? One factor which does help to decide urgency of appointment is the inclusion of visual acuity on the referral letter, and general practitioners should be encouraged at every opportunity to provide this information.

The second largest group investigated was that of patients with diabetic retinopathy. Fluorescein angiography was useful in differentiating between cystoid macular oedema and ischaemic maculopathy, and therefore whether laser therapy was indicated. On the whole, it proved unhelpful in the diagnosis and treatment of circinate retinopathy, but in one case two leaking sites were found on FFA rather than the one obvious clinically.

Previously it has been reported that the most commonly missed diagnoses which fluorescein angiography has corrected are branch retinal vein occlusion, chronic central serous choroidopathy, and retinal artery aneurysm with subretinal or subhyaloid haemorrhage.[11] This study found six cases of branch retinal vein occlusion and one aneurysm, as well as several cases of pigment epithelial detachment and preretinal gliosis, all clinically misdiagnosed as disciform macular degeneration.

In conclusion, although it is still very difficult to quantify the clinical value of fluorescein angiography, it is possible to make an attempt in conditions such as macular degeneration, and in this age of medical audit some attempt to assess the value and limitations of a relatively costly and time consuming investigation (which bears some risk to the patient) must be made. The study does show the circumstances in which fluorescein angiography is useful and where unnecessary angiograms could be reduced. Several patients with dry macular degeneration need not have had FFAs. None of the patients with unexplained poor visual acuity showed any abnormality, suggesting that it is not very useful in such cases, and only one of the five FFAs performed for circinate retinopathy influenced management. If one could cut down on unnecessary FFAs, this would reduce the waiting time for the investigation.

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# North Carolina's dominant progressive foveal dystrophy: how progressive is it?

Kent W Small, John Killian, Walter C McLean

**Abstract**

**We studied 34 family members at risk of having dominant progressive foveal dystrophy of Lefler, Wadsworth, and Sidbury (also called North Carolina macular dystrophy) and found 17 to be affected. Fifteen of these affected subjects were observed over at least a 10-year period for evidence of progressive macular degeneration. Only one subject showed objective evidence of progressive deterioration in only one eye. Our findings further substantiate that this dystrophy generally has a stable course, contrary to its original description.**

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Lefler, Wadsworth, and Sidbury[1] in 1971 reported on 25 affected members of a family with a dominantly inherited macular dystrophy. They described marked ophthalmoscopic variability from one individual to another. Asymptomatic subjects had only 'mild pigmentation' in the macula, while those subjects with subnormal visual acuity all had ophthalmoscopically obvious macular abnormalities. The most severe cases were described as having macular 'colobomas'. In addition many of the family members had an associated aminoaciduria.

Frank and colleagues[2] further studied this same family and called the disease 'dominant progressive foveal dystrophy'. They reported on a total of 50 affected subjects and categorised the macular appearance into three clinical stages which were said to progress from one stage to the next. Stage 1 maculae were described as 'scattered drusen and pigment dispersion'; stage 2 as 'confluent drusen'; and stage 3 as 'choroidal atrophy'. Additional testing disclosed normal results on electroretinography, electro-oculography, and colour vision tests. However, the progressive nature of the maculopathy was not well documented. The aminoaciduria was found to segregate separately from the macular abnormalities, suggesting that the urine and macular conditions were genetically unlinked and/or inherited as different Mendelian traits.

Two further observations recorded by Frank and associates[2] subsequently became controversial. Their description of the stage 3 macular lesion did not mention the staphylomatous or colobomatous-type appearance of the macula, previously noted by Lefler and associates.[1] They also recorded the peripheral retina as 'normal'. These points helped to confuse its nosology when similar diseases were later reported.

Gass,[3] who later examined an unspecified number of affected subjects, called this disease 'North Carolina macular dystrophy (NCMD)'. He questioned whether or not the maculopathy was progressive, and he described the most severe lesions as 'staphylomatous appearing' and the peripheral retina as abnormal. His observations were in apparent conflict with those of the earlier reports.[2]

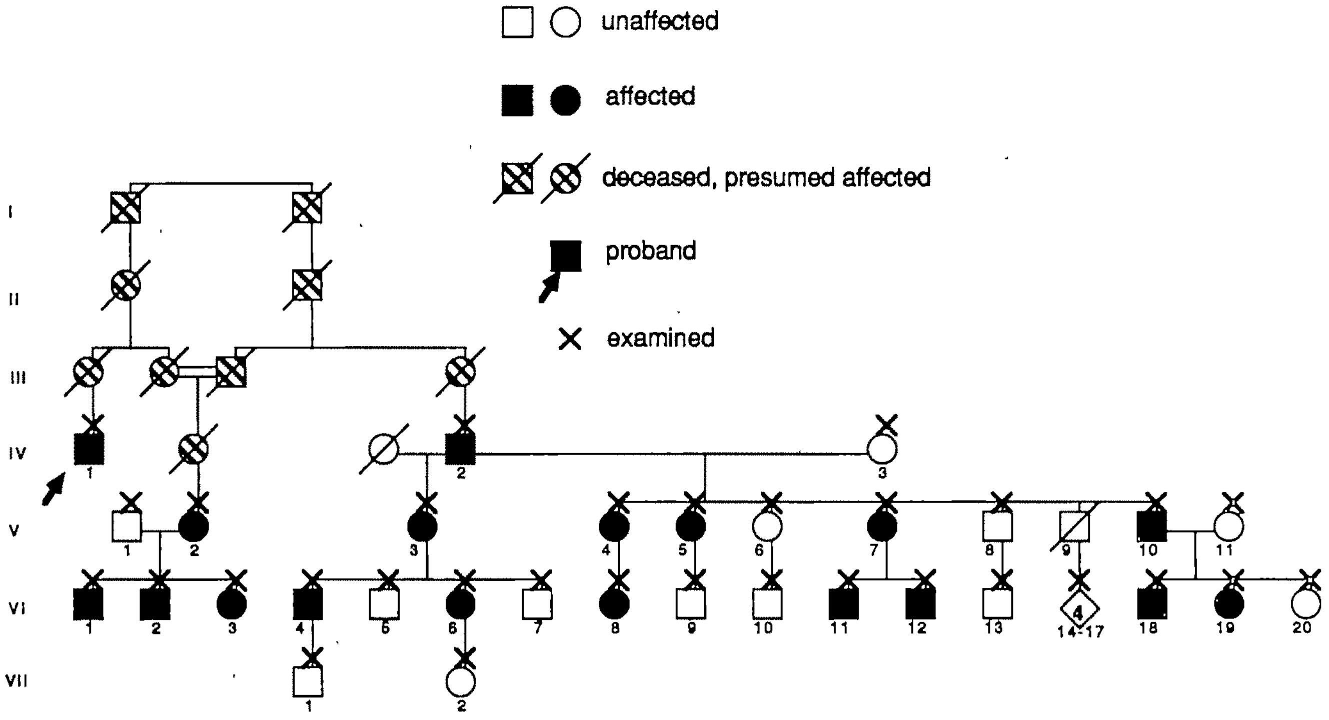

*Figure 1 Abbreviated pedigree, relationship of original NCMD proband to remainder of family shown.*

*Table 1* *Summary of results*

| *Pedigree* | *Grade of macular lesion* | *Age at 1st examination* | *VA at 1st examination* | *Age at latest examination* | *VA at latest examination* | *Progression* |
|---|---|---|---|---|---|---|
| VI–11 | 1 | 6 | 20/20–<br>20/20– | 16 | 20/20–<br>20/20– | No |
| VI–6 | 1 | 28 | 20/20–<br>20/30 | 38 | 20/20–<br>20/30 | No |
| VI–7 | 1 | 7 | 20/20<br>20/20 | 17 | 20/20<br>20/20 | No |
| V–7 | 1 | 22 | 20/20–<br>20/20– | 33 | 20/20<br>20/20 | No |
| VI–8 | 2 | 7 | 20/30<br>20/50 | 17 | 20/25<br>20/30 | No |
| V–5 | 2 | 16 | 20/20–<br>20/100 | 27 | 20/20<br>20/200 | Subjective |
| V–4 | 2 | 27 | 20/30<br>20/30 | 38 | 20/30<br>20/30 | No |
| VI–19 | 2 | 5 | 20/30<br>20/30 | 16 | 20/20<br>20/25 | No |
| VI–4 | 2 | 18 | 20/20<br>20/40 | 29 | 20/20<br>20/40 | No |
| VI–1 | 2 | 6 | 20/25<br>20/25 | 27 | 20/20–<br>20/20– | Subjective |
| VI–18 | 2 | 3 | 20/30<br>20/30 | 14 | 20/50<br>20/200 | Objective |
| V–10 | 3 | 29 | 20/30–<br>20/40 | 40 | 20/30<br>20/30 | No |
| VI–2 | 3 | 6 | 20/40<br>20/60 | 26 | 20/30<br>20/50 | No |
| V–2 | 3 | 25 | 20/50<br>20/90 | 51 | 20/40<br>20/100 | No |
| VI–3 | 3 | 6 | 20/50<br>20/100 | 30 | 20/40<br>20/80– | No |
| IV–2 | 3 |  |  | 80 | 20/60<br>20/60 | No |
| V–3 | 3 |  |  | 56 | 20/50<br>20/50 | No |

Pedigree=individual in figure 1.VA=Snellen visual acuity, age in years.

From 1974 to 1989 no further reports of studies of this family appeared. We recently reascertained the original NCMD family to begin clearing up some of these controversies. In our preliminary report[4] of 22 affected family members who had been examined 15-20 years earlier by Lefler *et al*[1] and Frank *et al*[2] we found only one subject who showed evidence of progressive visual deterioration in one eye. In the remaining 21, clinical course was stable. Furthermore, our fundus findings corroborated those of Gass.[3] The severe cases were clearly excavated, colobomatous, or staphylomatous in appearance when examined with binocular methods. The peripheral retinae had yellow specks at the level of the retinal pigment epithelium which resembled drusen. We now report our findings in an additional 17 affected family members to provide additional data on the clinical course of NCMD.

## Materials and methods

An extensive family history was obtained from 34 family members (17 affected) who were not initially known to be related to the original NCMD kindred. It became apparent that these subjects were direct descendants of the same three Irish brothers who brought NCMD to the United States some time before 1790. Therefore these 17 affected family members were afflicted with NCMD as well. The relationship of the proband of the original NCMD pedigree to these newly found NCMD family members is shown in Figure 1.

Fifteen of the 17 affected family members were initially examined by us at least 10 years ago and followed up to the present time. The ophthalmic examinations performed 10 years ago consisted in recording best corrected visual acuity at a distance of 20 feet (60 cm), pupillary

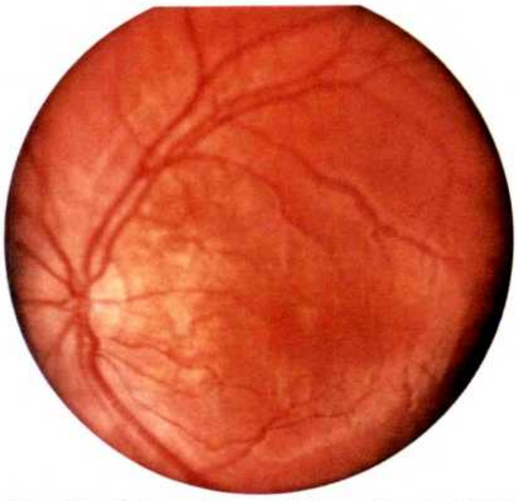

*Figure2A Right macula, grade 1, 6-year-old-male, VI–11, 20/20.*

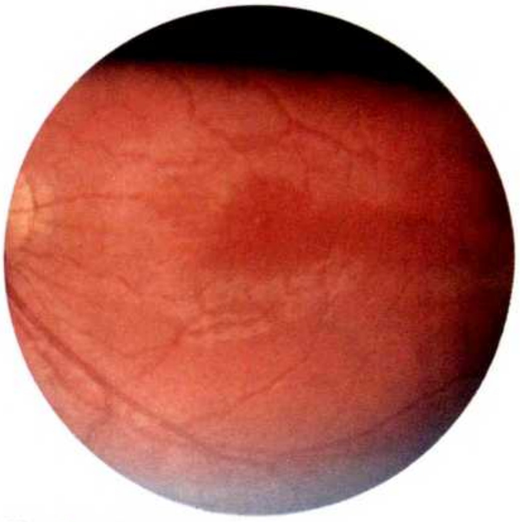

*Figure 2B Unchanged at 16 years old.*

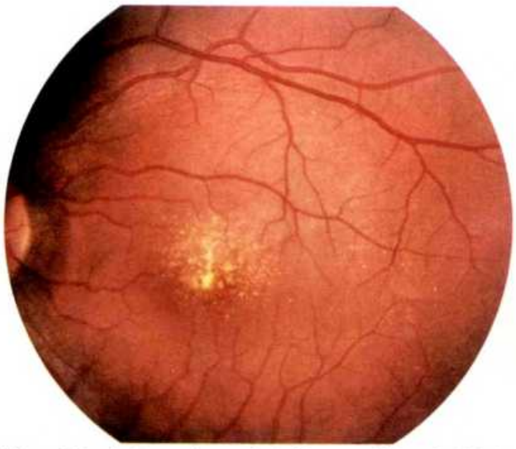

*Figure 3A Left macula, grade 1, 28-year-old female, VI–6, 20/30.*

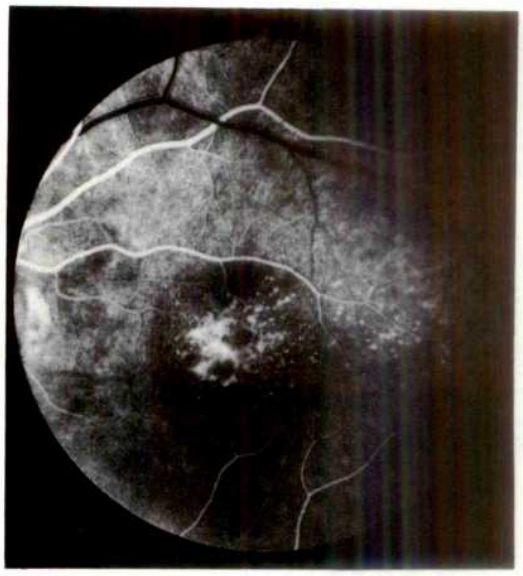

*Figure 3B Fluorescein angiogram, early phase with window defects which did not spread in later frames.*

reaction, slit-lamp examination, dilated fundus examination, and fundus photography. A fluorescein angiogram was performed on one subject. We performed the most recent ophthalmic examinations at home visits, recording visual acuity at near, namely 13 inches (33 cm) with the present spectacle correction, pupillary reactions, findings on dilated binocular indirect ophthalmoscopy, and the appearances on fundus photography with a hand held fundus camera. All affected subjects were asked whether they thought their vision had changed or been stable during their lifetime. Their visual acuities and fundus photographs from 10 years ago were compared with the recent findings for objective evidence of progressive macular changes.

## Results

The results are summarised in Table 1. Fourteen of the affected subjects' ages ranged from 3 years to 29 years at the time of the initial examination. Ten of them were 18 years old or less at the time of their initial examination and therefore presumably at the greatest risk of having advancing disease.

We categorised the maculopathy according to a similar classification system used in our recent report.[4] However, we are now referring to the gradation of the macular severity as 'grades' instead of 'stages' to emphasise further the stable nature of this disease. Four of the 17 affected subjects had grade 1 NCMD (Figs 2, 3) which consisted of only a few small flat yellow specks at the level of the retinal pigment epithelium. This was variably associated with pigment irregularity in the fovea. Grade 2 dystrophy (Figs 4–7) showed as confluent yellow specks at the level of the retinal pigment epithelium in the central macula. This was present in seven subjects. In the more severely affected grade 2 eyes (figs 6, 7), the maculopathy had a disciform appearance.

Grade 3 maculopathy (Figs 8, 9), present in six subjects, consisted of a discrete, well circumscribed, single, large (1–2 disc diameters) central macular excavation. The overlying neurosensory retina appeared intact as shown by the retinal vasculature draping over the sharp edge and dipping down into the crater. The absent or depigmented retinal pigment epithelium in the centre of the lesion was well demarcated. The only remnant of the choroid consisted of a few large choroidal vessels. The peripheral retinae of all affected subjects showed variable yellow specks and pigment irregularities also at the level of the pigment epithelium. Their visual acuities ranged from 20/20 to 20/200, median 20/30.

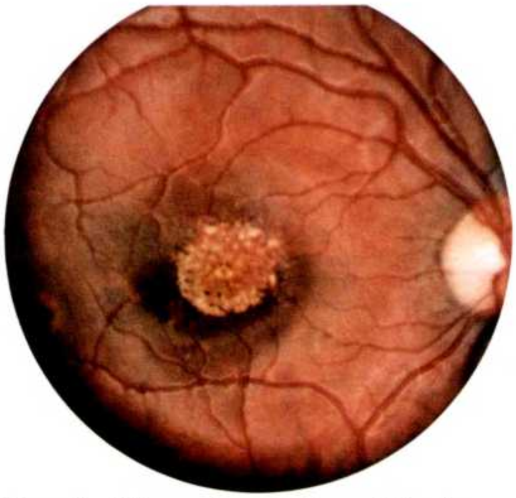

*Figure 4A Right macula, grade 2, 7-year-old female, 20/30, VI-8.*

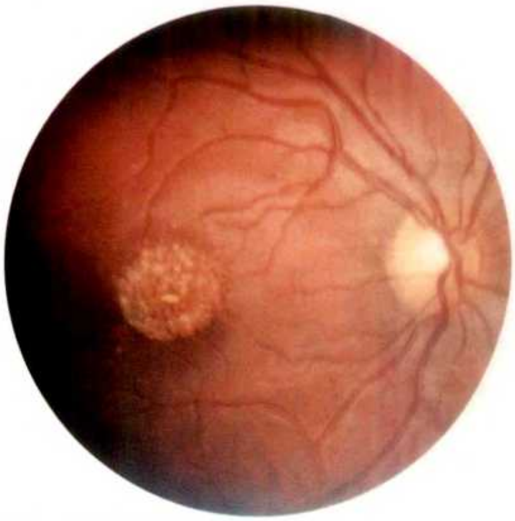

*Figure 4B Unchanged at 17 years old.*

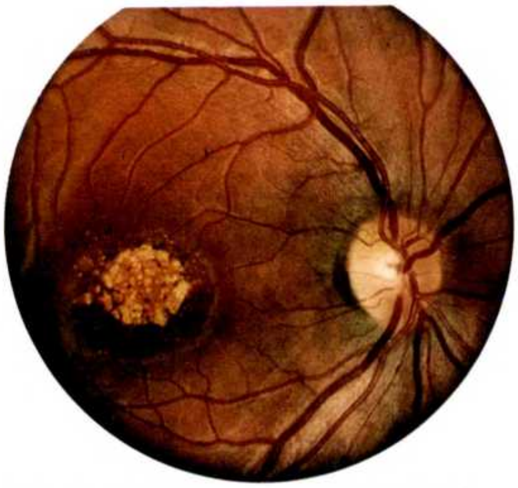

*Figure 5A Right macula, grade 2, 16-year-old female, 20/30, V–5.*

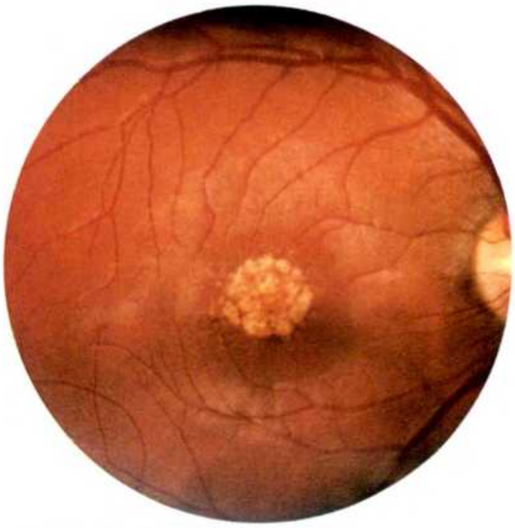

*Figure 5B Unchanged at 27 years old.*

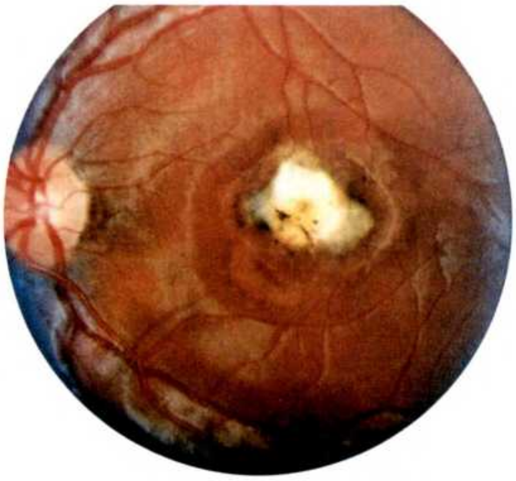

*Figure 6A Left macula, grade 2, 16-year-old female, 20/100, V–5.*

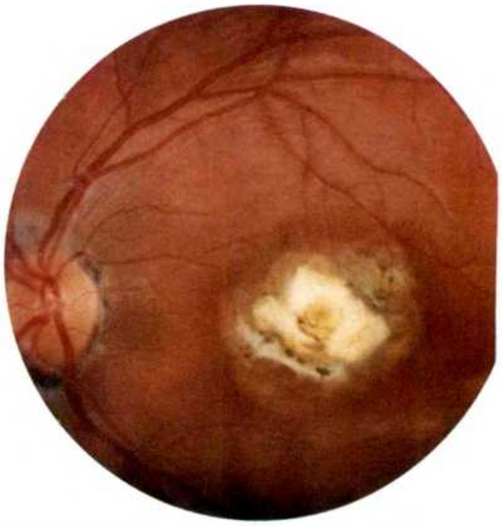

*Figure 6B At 27 years old, minimally increased pigmentation.*

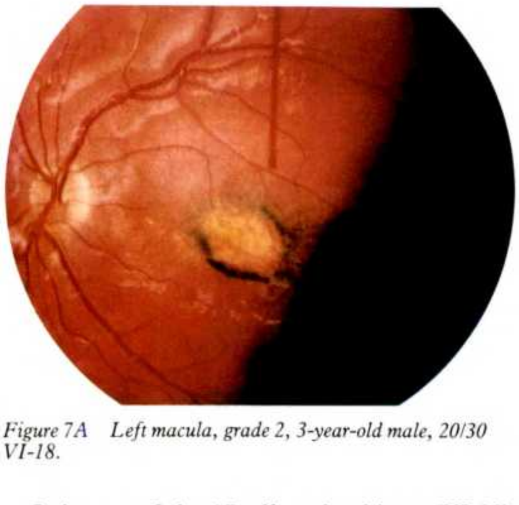

*Figure 7A Left macula, grade 2, 3-year-old male, 20/30 VI-18.*

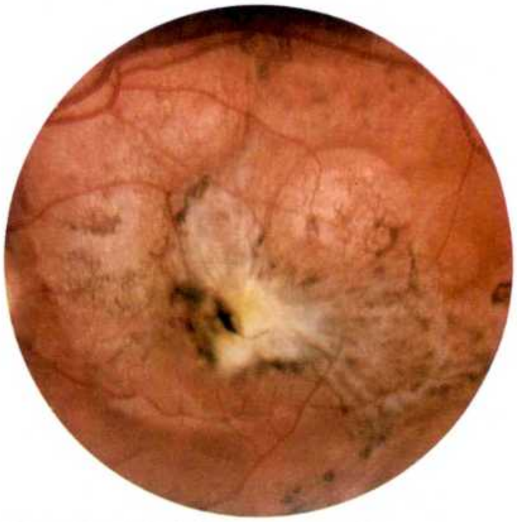

*Figure 7B Marked change by 14 years old, 20/200.*

Only one of the 17 affected subjects (VI-18) had objective progression of the disease. In his left eye the visual acuity dropped from 20/50 at 3 years of age to 20/200 by 13 years. The visual acuity in his right eye had remained stable around the 20/40 level during this time. The fundus photographs of the left eye also displayed changes consistent with the decreased vision (Figs 7A, 7B). A central white disciform lesion enlarged somewhat but probably more significant was the large (1 disc diameter) halo of retinal pigment epithelial irregularity surrounding it. This halo resembled a 'high water mark', as though submacular fluid had been present at an earlier time. No subretinal blood, exudates, or fluid could be found as evidence of an active choroidal neovascular membrane.

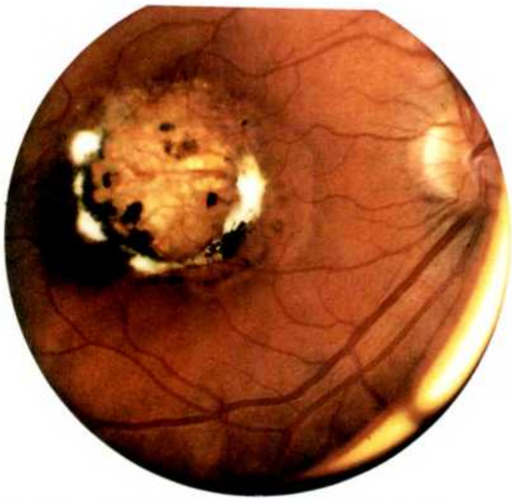

*Figure 8A Right macula, grade 3, 29-year old male, 20/30-, V–10.*

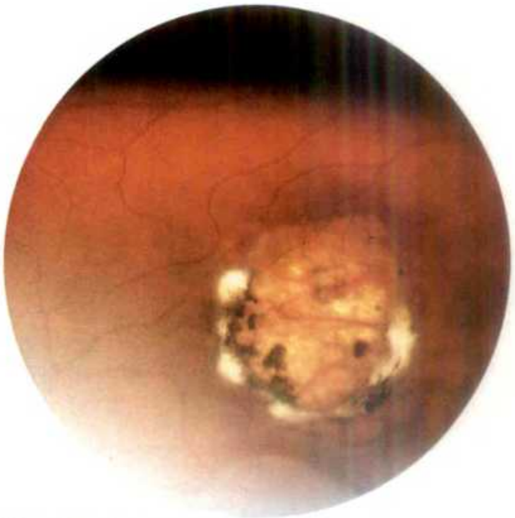

*Figure 8B Unchanged at 40 years old.*

Our previously reported subject[4] whose disease progressed was 17 years old at the time. From only these two subjects we cannot pinpoint the age at greatest risk for the rare event of disease progression any better than 'early in life'.

The remaining subjects had no objective change in either their visual acuity or the appearance of the macular lesions as judged by comparing the recent and the old fundus photographs. However, subjective change in visual acuity was noted by two subjects who complained of a brief period (1–2 weeks) during which they described a change in the size or shape of a previously noted central scotoma. These perceived changes did not, however, affect their Snellen visual acuity. Particularly noteworthy was that none of the 17 affected subjects experienced a continual progressive downhill course of their vision.

## Discussion

Dominant progressive foveal dystrophy of Lefler, Wadsworth, and Sidbury,[1] more recently called North Carolina macular dystrophy (NCMD)[3 4] (McKusick No 136550),[15] is an autosomal dominant macular dystrophy with complete penetrance and highly variable expressivity. This dystrophy has its onset during infancy or possibly even in utero as shown by a 3-month-old boy who had been previously found to have the grade 3 macular lesion. Those affected may range from being completely asymptomatic with 20/20 visual acuity to have a central scotoma with 20/200 visual acuity in the worse cases.

From this longitudinal study of 17 affected family members, our report provided further evidence that 'dominant progressive foveal dystrophy' of Lefler, Wadsworth, and Sidbury (NCMD) generally has a stable clinical course and is not progressive as orginally described by Frank *et al*[2] The results of our present study combined with the results of the 22 affected original NCMD family members we recently reported[4] revealed a 5% (2 of 37) incidence of affected individuals who experienced progressive macular deterioration in one eye. These two subjects, who experienced further deterioration, had grade 2 disease with a hypertrophic disciform appearance. Despite this, we have been unable to witness an active choroidal neovascular membrane or its sequelae such as subretinal blood or exudates in any of the 37 affected subjects. We suspect that these severe grade 2 lesions are somehow unstable, teetering between a grade 2 and grade 3 lesion. Perhaps this more severe macular dysfunction is caused by transudation of fluid across developmentally compromised retinal pigment epithelium and/or Bruch's membrane. Although age related macular

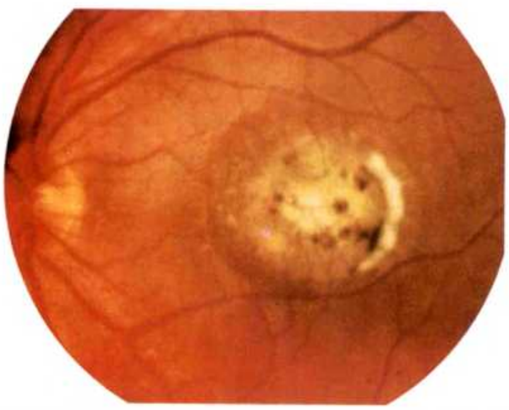

*Figure 9A Left macula, grade 3, 20-year-old male at time of photograph, 20/60, VI–2.*

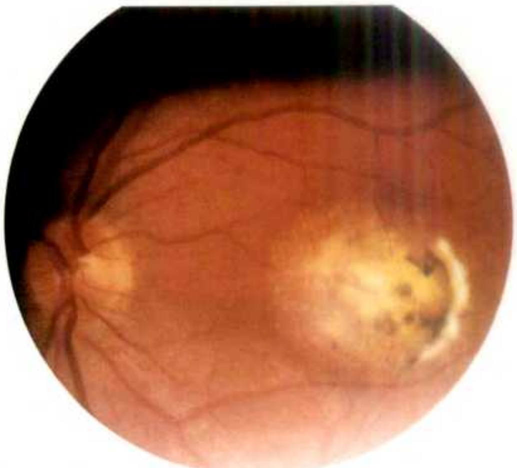

*Figure 9B Unchanged at 26 years old.*

*Table 2 Review of similar dominant macular dystrophies*

| *Disease* | *Youngest age detected* | *Progression* | *VA* | *Staphyloma macular* | *Peripheral retina* | *ERG* | *Colour vision* |
|---|---|---|---|---|---|---|---|
| North Carolina[1-4] macular dystrophy | 3 months | 2 of 78 eyes | 20/20 to 20/20 | Yes | Abnormal | Normal | Normal |
| CAPED[5] | 1 year | 2 of 14 eyes | 20/20 to 6/200 | Yes | NS | Normal | Normal |
| Dominant CAPED[6] | 7 years | 1 of 8 eyes | 20/20 to 20/200 | Yes? | NS | Normal | Normal |
| Autosomal dominant central pigment epithelial dystrophy[7] | 6 years | 1 of 8 eyes | 20/20 to 10/200 | NS? | Abnormal | Normal | Normal |
| Dominant slowly progressive macular dystrophy[11] | 46 years | 5 of 35 eyes | 20/20 to 20/200 | No | NS | Normal to abnormal | Normal |
| Dominant macular subretinal neovascularisation[10] | 26 years nyctalopia in childhood | 10 of 10 eyes | 20/25 to HM | No | Abnormal | Abnormal | Normal |
| Sorsby's pseudoinflammatory dystrophy[12 13] | 20s nyctalopia | Uniformly | 20/20 to CF | No | Abnormal | Normal to abnormal | Tritan defect |
| Sorsby's syndrome[14] | 7 years | 6 of 6 eyes | 20/120 to 20/180 | Yes | NS | NS | NS |
| Central retinal pigment epithelial dystrophy[9] | 17 years | 2 of 8 eyes | 20/16 to 20/200 | No | Normal | Normal | Normal to abnormal |
| Familial macular coloboma[8] | Infancy | 0 to 4 eyes | 20/200 | Yes | NS | Abnormal | Abnormal |

CAPED=central areolar pigment epithelial dystrophy. VA=visual acuity. ERG=electroretinogram. HM=hand motions. CF=counting fingers. NS=not stated in article.

degeneration is a phenocopy of grade 1 and 2 NCMD, we are reluctant to presume that the hypertrophic lesions (Figs 6, 7) were in fact due to a neovascular process.

We propose that the name 'dominant progressive foveal dystrophy'[2] is not appropriate. After our genealogical research into the original NCMD family the pedigree now consists of over 1400 individuals who are either affected or who are at risk of having NCMD. Because over 80% of this pedigree consists of Irish descendants living in North Carolina, we suggest that the proper designation for this dystrophy should be 'North Carolina macular dystrophy (NCMD)'. If a patient with this disease is found living in Ireland, then the name should probably be changed to Ireland/North Carolina macular dystrophy. With this name for the disease a patient encountered with a similar dominant macular dystrophy would more likely be questioned for relatives in Ireland or the North Carolina mountains. This additional family history might contribute to making the correct diagnosis.

Other possible names for NCMD are presumptive, such as 'central areolar pigment epithelial dystrophy'.[5-7] Equivalent names imply that the primary tissue affected is already known. Although clinically NCMD appears to be an abnormality of the retinal pigment epithelium, without histological or molecular confirmation such names should be held in reserve.

Three[5-7] other reported families with dominant macular dystrophies now seem likely to have the same disease as NCMD (Table 2). Central areolar pigment epithelial dystrophy,[5 6] central pigment epithelial and choroidal degeneration,[7] and NCMD had many common features. All were dominantly inherited, detected at young ages, and showed highly variable maculopathies within the families. These macular abnormalities spanned the spectrum from mild forms with a few 'drusen' in the fovea to severe macular 'colobomas' and 'staphylomas' with 20/200 visual acuities. These three dystrophies also generally had a stable clinical course. In central pigment epithelial and choroidal degeneration[7] the peripheral retina was abnormal, similar to that in NCMD. In the other two dystrophies[5 6] no mention was made of the appearance of the peripheral retinae. In all three[5-7] of these dystrophies the findings on electroretinography, electro-oculography, and dark adaptation and colour vision testing were also normal.

Other dominantly inherited macular dystrophies[8-14] clinically distinct from NCMD have a later age of onset.[10-12] Abnormal findings in electrophysiological and colour vision tests were also helpful in distinguishing these other dystrophies from NCMD.[8 10 12-14]

1 Lefler WH, Wadsworth JAC, Sidbury JB Jr. Hereditary macular degeneration and amino-aciduria. *Am J Ophthalmol* 1971; **71:** 224–30.

2 Frank HR, Landers MB III, Williams RJ, Sidbury JB. Dominant progressive foveal dystrophy. *Am J Ophthalmol* 1974; **78:** 903–16.

3 Gass JDM. *Stereoscopic atlas of macular diseases.* 3rd ed. St Louis: Mosby, 1987: 98–9.

4 Small KW. North Carolina macular dystrophy, revisited. *Ophthalmology* 1989; **96:** 1747–54.

5 Hermsen VM, Judisch GF. Central areolar pigment epithelial dystrophy. *Ophthalmologica* 1984; **189:** 69–72.

6 Fetkenhour CL, Gurney N, Dobbie JG, Chromokos E. Central areolar pigment epithelial dystrophy. *Am J Ophthalmol* 1976; **81:** 745–53.

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15 McKusick VA. *Mendelian Inheritance in man:* Catalogue autosomal dominant, autosomal recessive and X-linked phenotypes. 9th ed. Baltimore and London: Johns Hopkins University Press, 1990: 340.

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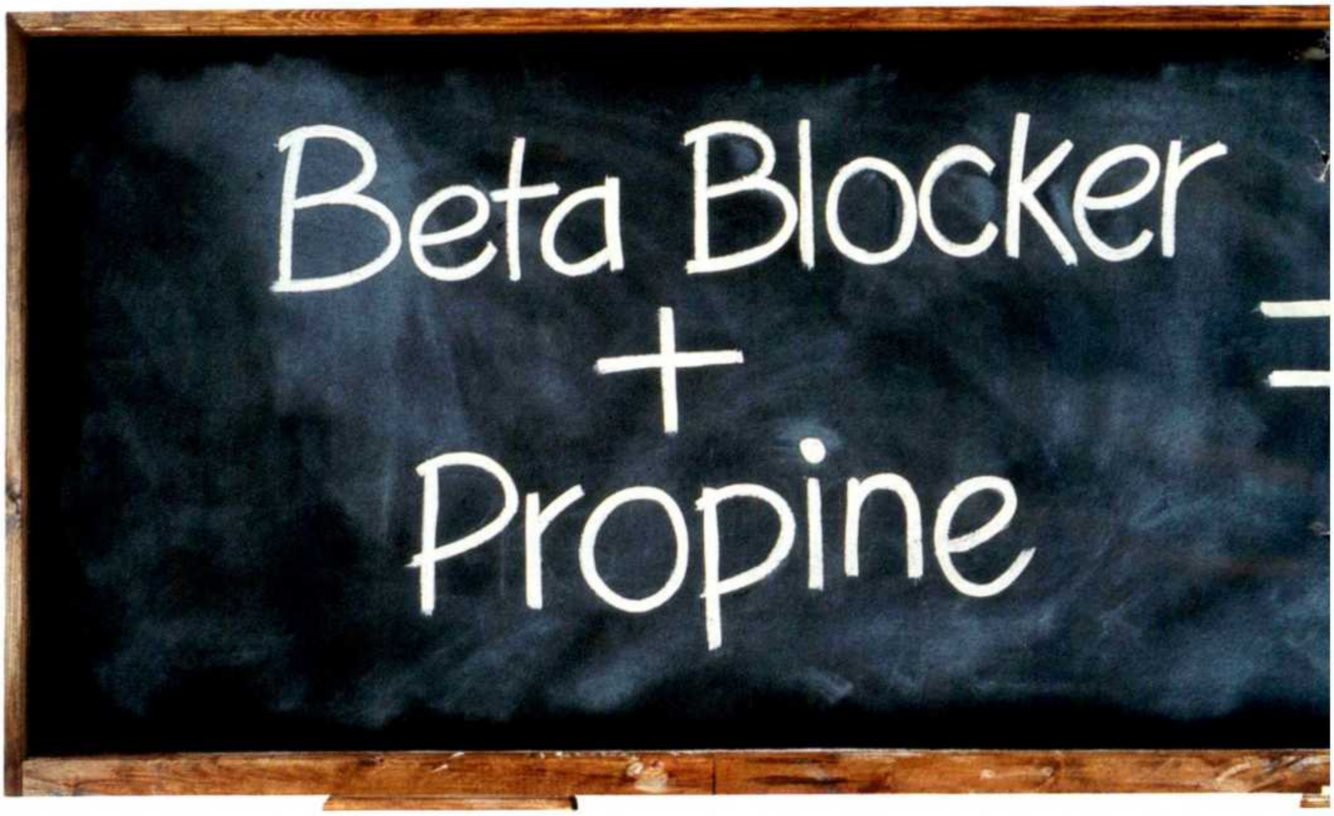

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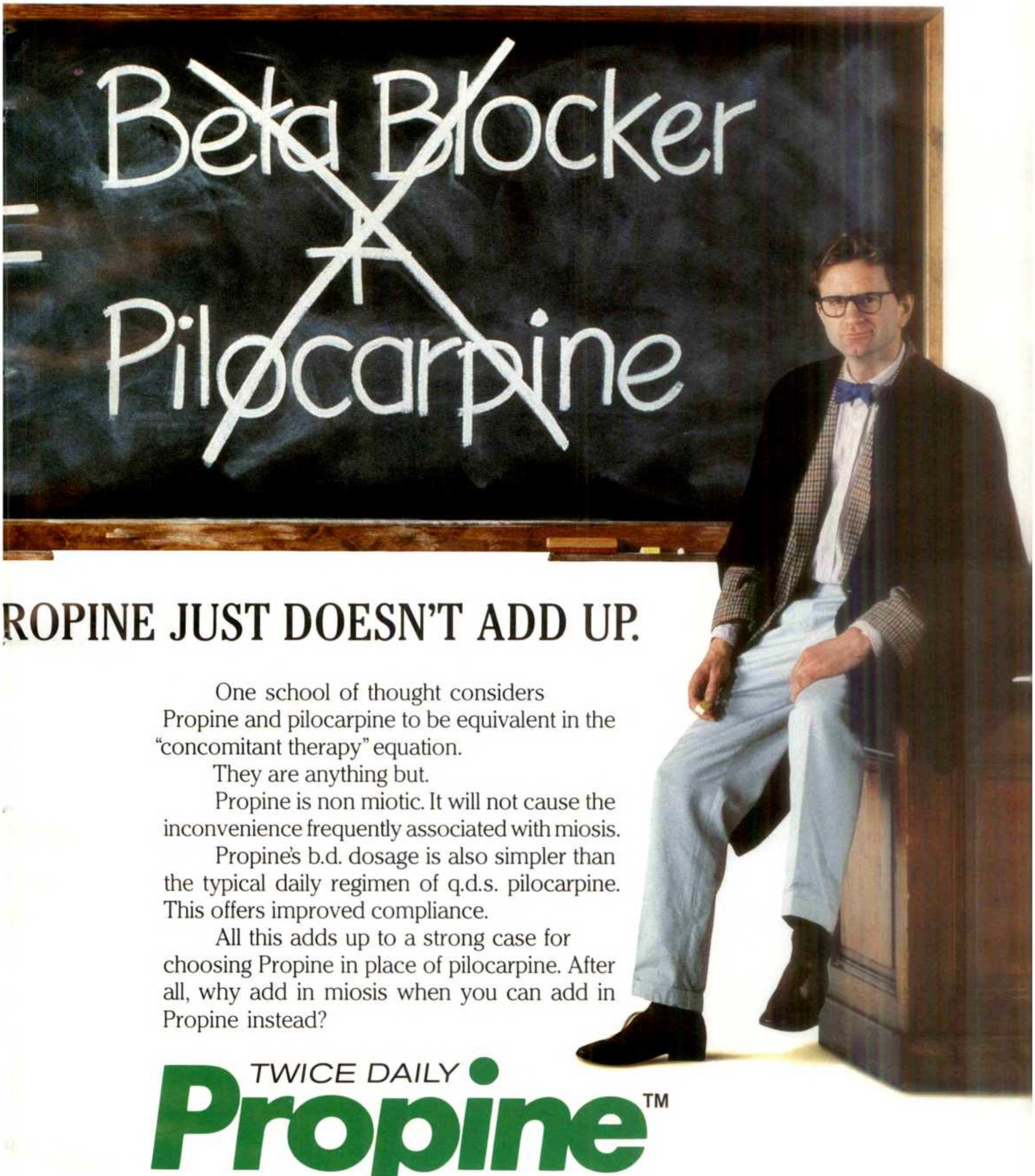
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# Cis-platinum chemotherapy for ocular basal cell carcinoma

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## Abstract

**We have used intravenous cis-platinum chemotherapy in the treatment of three patients with basal cell carcinoma of the lid extending into the orbit. Cis-platinum chemotherapy caused a reduction in tumour size and thereby delayed surgery in all cases. It allowed for local resection in one case, appeared to delay a patient's exenteration in a second case, and was used prior to radiotherapy in a third case. While not curative, cis-platinum may be useful as an adjuvant to decrease tumour mass prior to local excision and for patients who refuse or must delay exenteration.**

Basal cell carcinoma is the commonest malignant tumour of the eyelids.[1] Surgical excision is the treatment of choice because of the high rate of cure and excellent cosmetic and functional results.[2-14] However, there are circumstances when surgical resection is impossible or when a patient refuses to have surgery. Other forms of treatment have been described including radiotherapy, chemotherapy, phototherapy, drug therapy, immunotherapy, and cryotherapy.[15-24] Radiotherapy has been successful in the treatment of basal cell carcinoma, but associated lash loss, dry eye, keratopathy, cataract, retinopathy, and optic neuropathy have been reported.[15 16] While cryotherapy has been used for small superficial tumours, newer methods including immunotherapy, phototherapy, and drug therapy are still being investigated.[20-25]

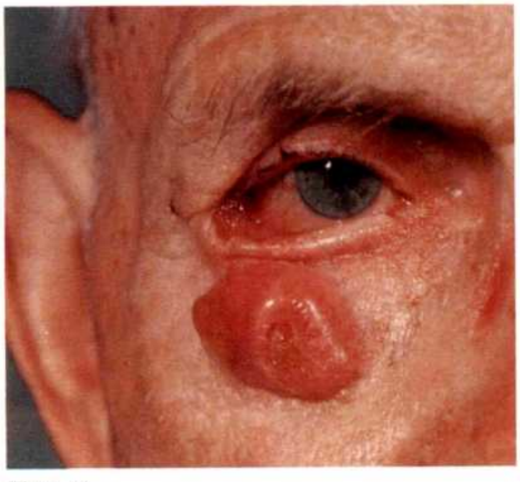

*Figure 1A*

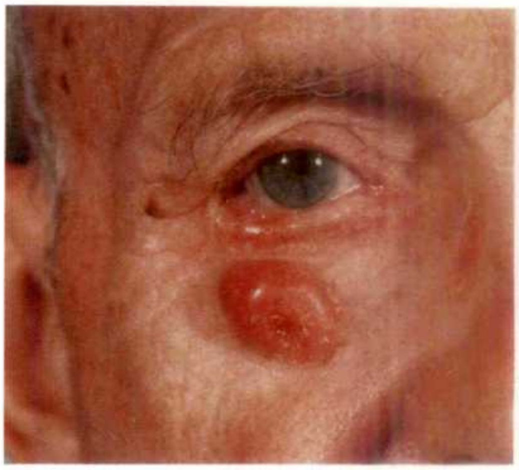

*Figure 1B*

*Figure 1(A) A pretreatment external photograph of the nodular basal cell carcinoma on the right lower lid (15 August 1985). Note the tumour-associated lateral ectropion. (B) A post-treatment external photograph of the nodular basal cell carcinoma on the right lower lid two months after the onset of intravenous cis-platinum chemotherapy (15 October 1985). Note the marked reduction in size of the superficial tumour and partial resolution of the lateral ectropion.*

Chemotherapy of basal cell carcinoma has also been tried as treatment for tumours involving the orbit and adnexa.[17-19] A total of eight cases of chemotherapy as a primary treatment for basal cell carcinoma in the eyelids have been reported.[17 18] We describe our experience in treating three cases of basal cell carcinoma involving the orbit and eyelids with intravenous cis-platinum.

## Materials and methods

Three patients with biopsy proved basal cell carcinoma and who refused exenteration were offered chemotherapy as a possible alternative to surgery. Our treatment protocol was a variation of that described by Luxenberg and Guthrie.[17 18] The patients were admitted to hospital and followed up by an ophthalmologist and medical oncologist. On admission the height and weight were measured to calculate body surface area (BSA). Routine admission laboratory studies included creatinine clearance, sequential multiple analyser profile-20, prothrombin time, activated partial thromboplastin time, electrocardiogram, chest *x* ray, complete blood count, and urine analysis. Patients were hydrated with normal saline, 125 ml/h, overnight prior to chemotherapy. On the day of chemotherapy, 20% mannitol (100 ml) was administered intravenously, followed immediately by cis-platinum (75–85 mg/square metre BSA) run in over two hours. Vigorous hydration was continued for 24 hours. Dexamethasone phosphate 10 mg, metoclopramide 50 mg, diphenhydramine hydrochloride 50 mg, perchlorperazine edisylate 10 mg, and droperidol 5 mg were used to reduce the side effects of the cis-platinum. Fluid balance, electrolytes, and renal function were monitored after administration of chemotherapy. Patients were discharged within 48 hours after chemotherapy.

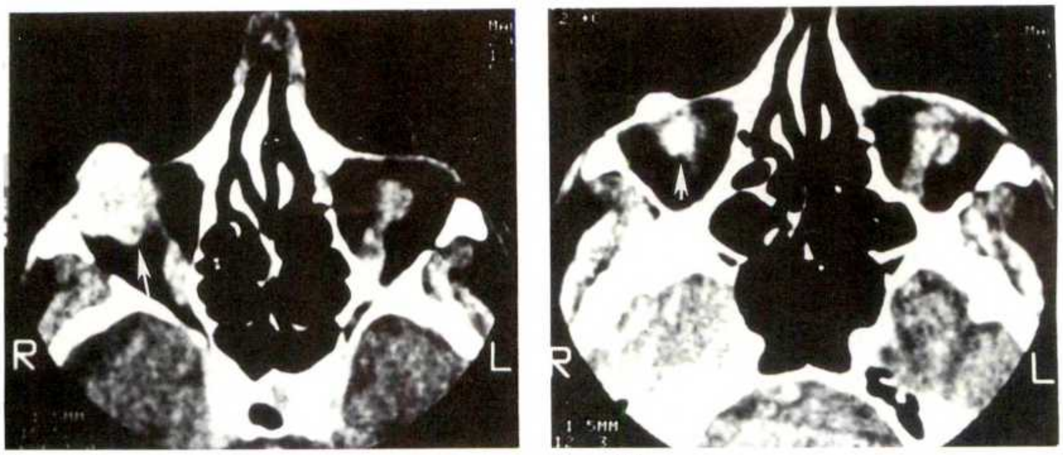

*Figure 2A* *Figure 2B*

*Figure 2(A) Pretreatment computed tomography of the orbit showing tumour invasion into the inferior and inferotemporal orbit (arrow). (B) Post-treatment computed tomography of the orbit showing a reduction in tumour volume (arrow).*

## Case reports

CASE 1

An 80-year-old white male presented in May 1985 with a two-year history of a right lower lid mass (Figs 1A). Ophthalmic examination revealed 20/40 vision in the right eye and full ocular motility. Slit-lamp biomicroscopy revealed a lateral ectropion and an extensive nodular tumour in the right lower lid. Computed tomography of the orbit demonstrated a mass on the right lower lid, extending into the inferior orbit to the level of the inferior rectus (Figs 2A). An incisional biopsy revealed basal cell carcinoma. Our patient refused surgical resection and was offered the alternative of cis-platinun chemotherapy.

Cis-platinum was administered without complication in July 1985. Two weeks later the tumour had regressed in size by approximately 30% (Fig 1B). A second course of cis-platinum was given in August 1985, and two weeks later the tumour was reduced in size by approximately 40%. We noted that the patient suffered mild, transient mental confusion associated with the chemotherapy and antiemetic therapy. Repeat computed tomography of the orbit confirmed a reduction in the size of the tumour (Fig 2B), and a third course of cis-platinum was administered in October 1985. Again treatment was complicated by transient night time mental confusion, this time requiring treatment with haloperidol. Because of the difficulty with therapy and the reduction in the size of the tumour and its intraorbital extent, this patient elected to proceed with local surgical excision in November 1985. An anterior orbitotomy and tumour excision with frozen section control provided negative margins. Then a modified semicircular flap with skin grafting was performed. Postoperative examinations showed no loss of vision and normal ocular motility. Permanent margins were negative for carcinoma. Follow-up reports four years later showed no evidence of recurrence.

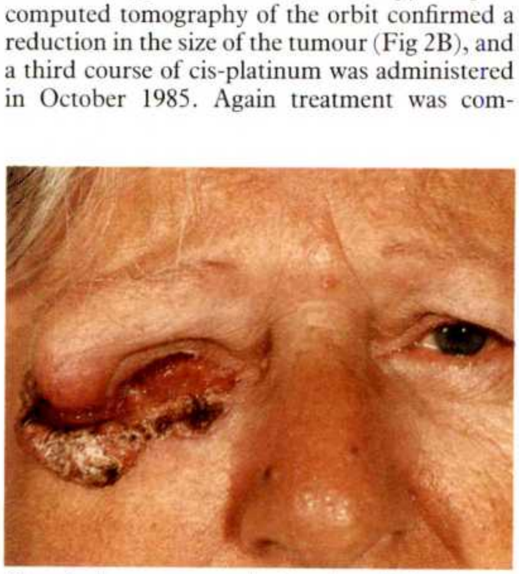

*Figure 3 Large mass extending from the medial canthus across the entire lower lid to 5 mm beyond the lateral canthus.*

CASE 2

A 66-year-old white female presented in August 1985 with a five-year history of a mass on the right lower lid. Ophthalmic examination showed a visual acuity of 20/20 in the right eye with restriction of infraduction. A large mass extended from the medial canthus across the entire lower lid to 5 mm beyond the lateral canthus (Fig 3). An incisional biopsy revealed basal cell carcinoma. Computed tomography of the orbit showed tumour invading the orbit, displacing the globe superiorly, and contiguous with the inferior rectus muscle. Surgical resection was refused. Cis-platinum chemotherapy was offered, and the patient received a course of intravenous cis-platinum in September and a second in November 1985. While partial regression was noted on clinical and repeat CT examinations, there was still obvious lid, conjunctival, and residual orbital involvement. Again surgical resection was recommended, and again the patient refused. In August 1986 she returned with pain and agreed to undergo exenteration.

CASE 3

A 68-year-old white male presented in December 1983 with a right lower lid mass present for one year. The lesion was noted to involve a 33 mm of the lower lid, and was diagnosed as an infiltrating morpheaform basal cell carcinoma by incisional biopsy. Sinus *x* rays and CT appearances of the orbit and sinuses were normal. He was treated with electron beam (external) radiation therapy and was irradiated with 5977 cGy in 30 fractions over 44 days in March 1984. The tumour appeared to respond well to the treatment, with complete regression of the visible part. Post irradiation epiphora and cicatrix formation with entropion were noted.

In May 1987, after three years of local control, the patient returned with recurrent basal cell carcinoma of the right lower lid and a mucoid discharge from the medial canthal area. The visual acuity in the right eye was 20/40 and he had full ocular motility. Computed tomography of the orbit revealed an abnormal soft tissue density anterior and medial to the globe with slight postseptal extension (Fig 4A). The ethmoidal and frontal sinuses showed mucosal thickening and bony erosion, with no evidence of tumour extension. An incisional biopsy was positive for basal cell carcinoma. Surgical resection was recommended, but since the tumour appeared to be localised to the nasal orbit a presurgical trial of cis-platinum chemotherapy was offered. The patient underwent three courses of chemotherapy in August 1987, September 1987, and November 1987 with reduction in the apparent size of the mass (Fig 4B). Since he developed severe akathisia after receiving metachlopromide with his first cycle of treatment, lorazepam was subsequently used as an antiemetic agent. The patient did not return for follow-up until June 1988, and a repeat biopsy again revealed basal cell carcinoma. Two additional cycles of chemotherapy were administered in July and September 1988. Then in December the patient was noted to have a rise in his creatinine level to 168 μmol/l and a reduction in his creatinine clearance to 46 ml/min. This precluded further chemotherapy.

We undertook extensive lid, orbit, and sinus resection in an attempt to excise the tumour. Multiple frozen sections were positive for tumour, and I-125 brachytherapy implants were placed in the frontal sinus and against the remaining ethmoidal sinuses as a 30 Gy boost to external radiotherapy. Then 60 Gy of external beam radiation was delivered to the orbit and sinuses. Eighteen months after radiotherapy there has been no evidence of new tumour growth.

## Discussion

This is the second series of cases recording a reduction in the size of basal cell carcinomas of the lids and orbit associated with cis-platinum chemotherapy. All three patients we treated were considered to have partial regression of their tumour. In one of the three cases partial regression allowed for local excision with negative margins, in another delayed exenteration, and in the third it postponed radiotherapy.

There are significant side effects associated with intravenous cis-platinum chemotherapy.[26-34] As seen in case 3 in our report, dose related and cumulative renal insufficiency is the major toxic effect.[26] Thus pre-existing renal insufficiency is a contraindication to its use. Careful attention to fluid status, creatinine clearance, and creatinine levels is mandatory.

Severe nausea and vomiting are frequently observed after the administration of cis-platinum, so that administration of antiemetics is standard practice. Two of our patients (cases 1 and 3) had neurological reactions to the combination of medicines used in this protocol. These reactions were probably due to the antiemetic therapy, not the cis-platinum. Ototoxicity has been observed in some patients, usually manifested by tinnitus or high frequency hearing loss.[27]

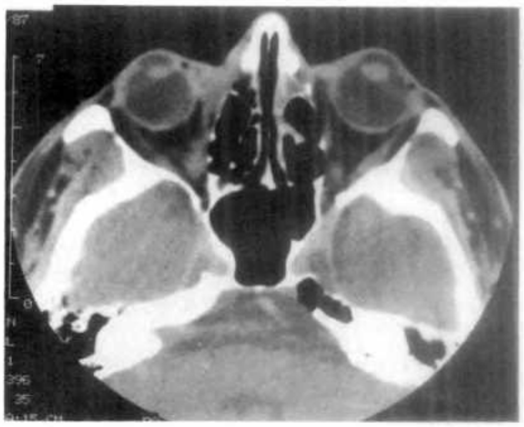

*Figure 4A*

*Figure 4(A) Computed tomography of the orbit showing an abnormal soft-tissue density medial and anterior to the globe. Postseptal extension is noted. Bone thinning and mucosal thickening was noted in the sinuses. (B) Post-treatment computed tomography of the orbit showing a reduction in the apparent size of the tumour after three courses of cis-platinum chemotherapy.*

There are a number of reports describing the ocular side effects of cis-platinum or chemotherapeutic regimens that contain cis-platinum: cortical blindness, optic disc swelling, retrobulbar neuritis, homonomous hemianopsia, retinal pigmentary changes, abnormalities of electroretinogram and visually evoked potentials and encephalopathy.[28-34]

While the preferred method of treatment of basal cell carcinoma is surgical excision, there are circumstances when that is impossible. Occasionally a patient refuses to have surgery. In cases where extensive surgery is refused, less extensive surgery coupled with an alternative treatment may be effective.

All three patients reported on here, including one who was pretreated with radiation therapy, had an objective response to treatment. No case attained complete remission, and all required

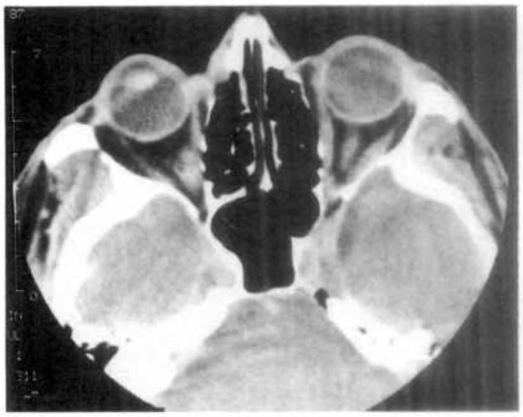

*Figure 4B*

further treatment. Our data confirm the observations of Luxenberg and Guthrie that lid and periocular basal cell carcinoma will respond to intravenous cis-platinum with adriamycin.[17 18] In their cases the commonest outcome was a partial reduction in tumour size requiring additional treatment to control tumour spread. Our experience was similar in that cis-platinum alone was not curative, yet it served as a helpful adjunct in the management of basal cell carcinoma of the eyelids and orbit.

The authors have no proprietary interest in the chemotherapeutic agent cis-platinum.

We thank Dr Frederick A Jakobiec, for his original suggestion to contact Dr Luxenburg, and Dr Jason Slakter, Dr Peter Small, Dr Jay L Bosworth, and Dr Samuel Packer for sharing in the care of these patients.

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*British Journal of Ophthalmology*, 1991, 75, 411–413

# Ocular responses in healthy subjects to topical bunazosin 0·3% – an $\alpha_1$-adrenoceptor antagonist

D R Trew, L A Wright, S E Smith

## Abstract

**The ocular effects of the α-adrenoceptor blocking drug bunazosin, administered as eyedrops, have been measured in a placebo-controlled double-blind single-dose study in 15 healthy volunteers. The drug significantly reduced intraocular pressure over 10 hours, and there was no associated change in pulsatile ocular blood flow. Characteristic effects of α-adrenoceptor blockade were observed – miosis, ptosis, and conjunctival hyperaemia. The miosis alone persisted for more than 24 hours in nine out of 15 subjects.**

Lowering of intraocular pressure by local sympathetic blockade[1] provides the commonest basis for the medical management of chronic simple glaucoma, in which pressure is usually high. Long term administration of β adrenoceptor antagonists successfully controls intraocular pressure,[2] yet in many patients visual field loss continues and vision deteriorates.[3] One factor which could be involved is a progressive diminution of the blood supply to the posterior segment of the eye. Timolol has been shown to cause vasoconstriction in human retinal arteries[4] and to have similar effects associated with a decreased blood flow to the optic nerve head and choroid in experimental animals.[5] We have previously shown that patients suffering from chronic open angle glaucoma have a reduced pulsatile ocular blood flow and that this was not improved by the use of topical timolol.[6] Agents which improve local circulation may help to prevent visual deterioration.

Bunazosin is a vasodilator, an analogue of the α receptor antagonist prazosin which is widely used in the treatment of systemic hypertension[7] and which has been found to lower intraocular pressure in animal studies by suppression of aqueous formation rather than a change in outflow.[8 9] Information of a similar nature is also available for topically applied bunazosin in a few human volunteers.[10] In these studies its topical application has been shown to cause minor irritation only.

The study of α-adrenergic receptors in the eye is receiving increasing interest, particularly in the field of glaucoma research. Recent reviews have highlighted the hypotensive effects of both antagonists[11] and agonists such as clonidine (α-2)[12], and these or related agents may well provide the basis for future therapeutic action.

In addition to their hypotensive action, α-adrenergic drugs may have an important effect on blood vessels in the eye, affecting supply to critical areas of the retina, choroid, and disc. Catecholamine binding sites have been demonstrated in the retinal vessels of animals,[13] though whether they are present in human eyes is not yet known.

The present study has been undertaken, therefore, to record the effects of topical application of bunazosin 0·3% on intraocular pressure and pulsatile ocular blood flow and to evaluate any disadvantages and risks associated with their use.

## Materials and methods

### SUBJECTS

Fifteen healthy subjects (seven male, eight female) aged 20-59 years were recruited to the study. All were of normal height and weight and none were found to have any abnormality on ocular, cardiovascular, and general medical examination or in haematological or biochemical profiles. Each gave written consent to participate, and the study was approved by the Ethics Committee of West Lambeth Health Authority.

### TREATMENTS AND STUDY DESIGN

Bunazosin 0·3% and a matching 'vehicle only' solution were administered double blind as eyedrops, one to each eye. The eyes were randomly assigned to bunazosin or vehicle eyedrops which were contained in identical and consecutively numbered vials for each subject. Formulation and packaging was performed by Dispersa Ltd, and the code was held by them throughout the trial.

Subjects attended on one occasion, in the morning. Two drops of either drug or vehicle solution were instilled 30 seconds apart to one eye and the same procedure followed for the second eye with the second numbered vial.

### MEASUREMENTS

The following measurements were performed before and at various times after eyedrop instillation:

(1) Pupil diameters were measured by infrared TV pupillography, after 30 seconds in darkness, with a Whittaker 1800 series pupillometer, prior to eyedrop instillation and at 1, 2, 6, 10, and 24 hours.

(2) Eyelid positions were recorded with a Yashica Dental-Eye camera with the subject's gaze at infinity. The palpebral height was measured, on projection, through the midpoint of the pupil. Measurements were performed prior to eyedrop instillation and at 1, 2, 6, and 10 hours.

(3) Intraocular pressure was measured by Goldmann applanation tonometry, under benoxinate 0·4% local anaesthesia, in the sitting

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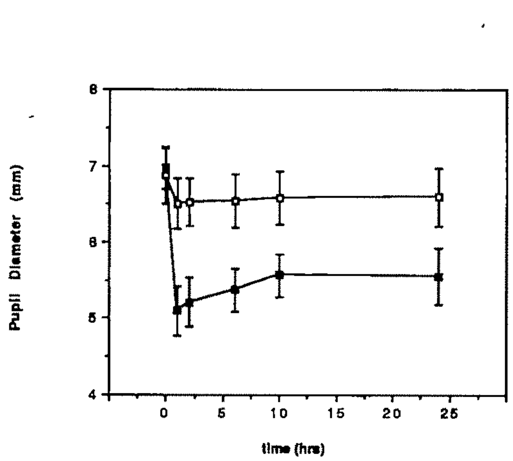

*Figure 1 Mean pupil diameters (mm) with standard errors, for bunazosin 0·3% treated (closed symbols) and vehicle-only treated eyes (open symbols) following eyedrop instillation.*

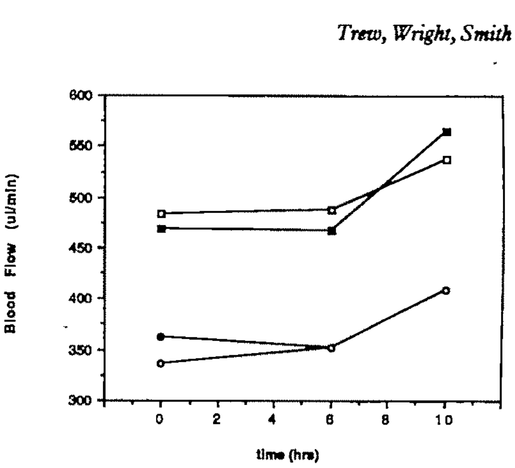

*Figure 3 Mean values for pulsatile ocular blood flows (µl/min) in the erect (square symbols) and supine (round symbols) positions. Other symbols as in Figure 1.*

position prior to eyedrop instillation and at 1, 2, 6, and 10 hours.

(4) Pulsatile ocular blood flow was calculated after measurement with a Langham pneumotonometric system in the erect and, after 15 minutes, in the supine positions prior to eyedrop instillation and at 6 and 10 hours.

(5) Adverse responses to the drops (local burning, pain, misting of vision, headache) were sought by direct questioning prior to instillation and then at 1, 5, and 10 minutes and 1, 2, 6, 10, and 24 hours. At the same times tearing and redness of the eyes were assessed by inspection and the responses graded according to the scale: 0=none, 1=mild, 2=moderate, 3=severe.

(6) Heart rate and blood pressure were recorded by standard methods.

### STATISTICAL ANALYSIS

Values for pupil diameter, palpebral height, intraocular pressure, and ocular blood flow were analysed by comparisons between the two eyes of each subject by Student's paired *t* test. The scaled measurements of ocular hyperaemia were ranked and subjected to a Wilcoxon signed rank test. Ocular discomfort and visual impairment, also recorded as discrete variables, were not analysed because so few positive responses were obtained.

## Results

*Pupil diameter.* Mean pupil diameters are illustrated in Figure 1. Miosis occurred in the drug-treated eyes and to a small extent in the untreated eyes. A significant drug effect ($p<0\cdot001$) was recorded from one hour to 24 hours after eyedrop instillation, but miosis was observed to persist in nine of 15 subjects for at least 48 hours.

*Palpebral height.* There was no significant change in palpebral height in either eye alone following eyedrop instillation. However, an interocular difference was detectable at 1 hour (0·7 mm mean, $p<0\cdot01$) and 2 hours (0·6 mm mean, $p<0\cdot01$) following treatment, demonstrating that bunazosin reduced palpebral height, causing a small degree of ptosis.

*Intraocular pressure.* The drug significantly reduced intraocular pressure (Fig 2). A small effect was noted after only 1 hour following instillation, but the greatest mean pressure difference between treated and untreated eyes occurred at 6 hours (2·7, SEM 0·5, mmHg, $p<0\cdot001$) as measured by Goldmann tonometry.

*Pulsatile ocular blood flow.* No significant changes in pulsatile flow were recorded as occurring either with time following eyedrop instillation or between treated and untreated eyes. There was a small increase in blood flow during the course of the day in both drug-treated and untreated eyes and in both erect and supine positions (Fig 3).

*Symptoms and signs.* Bunazosin-containing drops produced significantly more conjunctival hyperaemia than did the vehicle-only drops, the effect being greatest during the period 10 min to 2 h (Fig 4). Some residual effect was present at

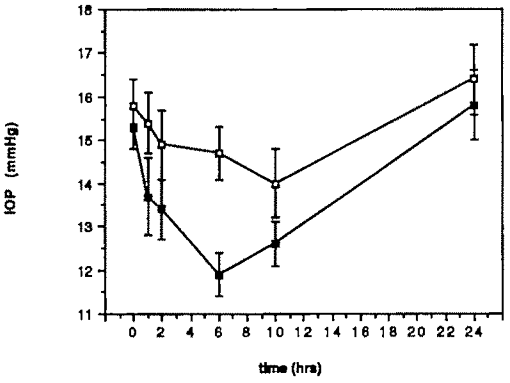

*Figure 2 Mean Goldmann intraocular pressures (mmHg) with standard errors for bunazosin treated and vehicle-only treated eyes following eyedrop instillation. Symbols as in Figure 1.*

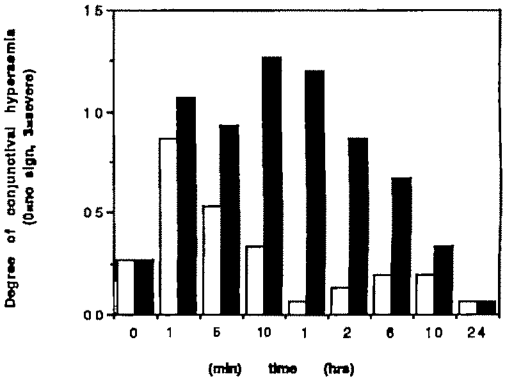

*Figure 4 Mean values for degree of observed conjunctival hyperaemia, scaled as indicated in 'Methods,' for bunazosin treated (hatched bars) and vehicle-only treated eyes (open bars) following eyedrop instillation.*

10 hours but had disappeared by 24 hours after eyedrop instillation.

Mild burning sensations were reported by 4/15 subjects, but any persistent sensation occurred equally between drug-treated and untreated eyes. Mild to moderate visual blurring was reported by 5/15 subjects, both eyes being equally affected.

*Blood pressure and heart rate.* No clear changes occurred in blood pressure during the course of the day. There was a small increase in the mean heart rate during the day in both the erect and supine positions, but in the presence of an almost unchanged blood pressure this was unlikely to be a drug effect.

## Discussion

This study has shown that topical bunazosin 0·3% reduces intraocular pressure, though the effect was modest and rather less than that produced by topical β-adrenoceptor antagonists, which usually have a faster onset and greater magnitude of action. There were no significant changes in pulsatile ocular blood flow in this study, but the drug was administered only once. Future studies may show that longer term usage has greater effects on the ocular vasculature and produces important measurable changes.

No serious side effects nor adverse drug reactions were reported, but the drug did induce characteristic features of α-adrenoceptor blockade in the eye, comprising miosis, partial ptosis, and conjunctival hyperaemia. These cosmetic effects are likely to influence compliance in clinical usage, but longer term studies in glaucoma patients are needed to find out if the magnitude of the ocular hypotensive action is sufficient to overcome this disadvantage.

We thank Dispersa Ltd for the gift of bunazosin 0·3% eyedrops and for generous financial support, including provision of the Langham ocular blood flow system DRT is supported by the Iris Fund for Prevention of Blindness and the Special Trustees of St Thomas's Hospital. LAW is supported by the Research (Endowments) Committee of West Lambeth Health District.

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# FIFTY YEARS AGO

### The empty socket

It has often struck us as odd that one does not find an ophthalmological subject used as an Inn sign in this country, but we do not know of a single case. Other anatomical subjects occur: *e.g.,* the hand often, the heart, occasionally. St. Peter's finger is met with in one instance. Arms are, of course, frequently found in this connexion, but here the significance is heraldic and not anatomical. The eye is very rarely met with in heraldry as we have observed before.

Care would be needed in giving an ophthalmic name to a pub, for if the house were called the 'evil eye' the more superstitious of the village inhabitants would give it a wide berth. And 'the squinting eye' would almost certainly become in local parlance the 'boss eye' and from that to 'boozy,' the transition is easy. Hardy would seem to have anticipated in a mild degree our need, for one of the village inns in 'Tess' was called the 'Pure Drop.' We fear that in this case he was thinking of a drop of drink and not of an eye drop.

The late Mr George Pollock, in lecturing on fractures at St George's Hospital more than half a century ago, used to tell an apocryphal story of a certain publican who changed the name of his house from the 'crooked billet' to the 'crooked arm.' This was done to annoy the local doctor who had had a bad result in the treatment of a case of fracture in one of the publican's children. The results on the practice were said to have been disastrous and the doctor had to leave the district. Fortunately for us the eye hardly lends itself to such a theme. We suggest our heading as a possible sign for an inn in the hope that some eminent English artist may feel inclined to draw a portrait of the oldest inhabitant minus one eye.

Annotation in *Br J Ophthalmol* 1941; 25: 130–1.

British Journal of Ophthalmology, 1991, 75, 414–416

# Emmetropisation, squint, and reduced visual acuity after treatment

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## Abstract

**In a sample of children used to assess the value of optical correction of hypermetropia from the age of 6 months the refraction of the most hypermetropic meridian frequently became less than 3·5 D as the children grew. When this occurred, the incidence of squint was significantly less ($p<0\cdot001$) and the last known acuity after treatment was significantly better ($p<0\cdot001$) than when it did not. This process of emmetropisation appears to have been impeded by the consistent wearing of hypermetropic spectacle correction from the age of 6 months.**

Fabian[1] first noticed that, if refractions were recorded as spherical equivalents, the wide range found in infants became narrower as the children grew. He called the process 'emmetropisation.' An example of this is the reduction of astigmatism that occurs after the age of 6 months.[2-7] The basic spherical refraction may not change significantly,[3 7] but our study of changes in the refraction of individual meridia between the ages of 1 and 3½ years[3] confirmed Fabian's observations if the initial level of hypermetropia was +2·50 D or less. However, if the level of hypermetropia in a given meridian was >2·50 D at 1 year, there was an almost even chance that the level of hypermetropia increased, not decreased.

When we assessed the results of our trial of optical correction of hypermetropia from the age of 1 year[8] we suspected two things: (1) the children who squinted were those who remained hypermetropic, but if the initial level of hypermetropia in a child decreased the prognosis for squint and amblyopia was better; (2) children drawn for treatment with spectacles appeared to remain hypermetropic. We could not prove either of these suspicions, principally because we did not know what was a 'normal' amount of hypermetropia at a given age. We therefore decided to look again for an association between reduction of hypermetropia and the visual outcome in children included in our recent trial of treating hypermetropia from the age of 6 months.[9] In order to do this we arbitrarily chose a level of hypermetropia below which we deemed that emmetropisation occurred. Since the criterion for entry into this trial was the level of hypermetropia in the most hypermetropic meridian of a pair of eyes, we continued to use this method of recording hypermetropia. We also report observations on the possible effect of wearing spectacles on the process of emmetropisation.

## Patients and methods

The sample of children is the one reported in our trial of treating abnormal hypermetropia with spectacles from the age of 6 months[9] in an attempt to prevent squint and amblyopia. Details of the protocol used to conduct that trial were reported in that paper.[9] Three hundred and seventy two infants, aged 6 months, with +4·00 or more dioptres hypermetropia in one or more meridia of either eye were randomly allocated treatment with spectacles or no treatment, and followed up as effectively as possible. If a child in either group developed a squint, or was found (usually at age 3½ years) to have reduced visual acuity, he/she was treated conventionally with spectacles, occlusion, or operation as appropriate. The presence of squint was diagnosed with the cover test. Visual acuity was recorded only with Linear Sheridan-Gardiner or Snellen tests. All the refractions were done by the same person (RMI) after cycloplegia with cyclopentolate 1%. The refraction reported is the amount of hypermetropia in the most hypermetropic meridian after +1·75 D has been subtracted from the retinoscopy findings of all meridia of a pair of eyes. Information abut the refractions, presence of squint, and the last known visual acuity after any additional treatment had been given is now available for 287 of the children.

The first purpose of this paper is to relate the reduction of hypermetropia that occurred after the age of 6 months to the presence of squint and the last known corrected visual acuity in the case of 143 children who were drawn for no treatment. Secondly, the changes of refraction of these children have been compared with those of the 144 children who were drawn to wear spectacles.

## Results

Since there are no published guidelines on how one could judge whether emmetropisation had occurred, or indeed by what age it should have occurred, we have had to set limits arbitrarily. The age of 3½ years was chosen as the time by which emmetropisation should have taken place if it was going to do so, but we could not stick rigidly to that time because 23 children drawn for no treatment were diagnosed as having convergent squint before 3½ years, and were treated with spectacles. Eighteen of these 23 children had +3·50 or more dioptres meridional hypermetropia when the squint was diagnosed, and there is a suggestion (see later in this paper) that treatment could have encouraged them to remain hypermetropic after glasses had been prescribed. Therefore, on the assumption that failure to reduce infantile hypermetropia soon enough might be a cause of squint, we decided to take the refraction at the age of 3½ years, *or* at the time a squint was diagnosed if that was before the child reached 3½ years in order to judge whether

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emmetropisation had occurred. Secondly, since we do not yet know what level of hypermetropia, in the most hypermetropic meridian of a pair of eyes, is 'normal' for a given age, we have arbitrarily chosen a figure of +3·50 D in any one meridian as the dividing line. Astigmatism and anisometropia have been ignored.

### EMMETROPISATION AND INCIDENCE OF SQUINT

Complete information is available on 143 children who were initially drawn for no treatment. From the figures shown in Table 1 it is clear that those children whose hypermetropia remained at or above +3·50 D had a higher incidence of squint. This difference is statistically significant ($p<0\cdot001$).

### EMMETROPISATION AND LAST KNOWN VISUAL ACUITY

We have not attempted to relate emmetropisation to whether a child did or did not have amblyopia, because it is difficult to define 'amblyopia' in terms of any given visual acuity. In addition some of these children had occlusion before their visual acuity could be accurately assessed. Therefore we record the last known acuity of the worse-seeing eye after all treatment, including occlusion, had been given. This is worse in the case of those children in whom emmetropisation was considered not to have occurred. The results are summarised in Table 2, and the difference is significant whichever way the figures are arranged for statistical analysis. As they stand, $p<0\cdot001$, but, if a dividing line is drawn between those whose last known acuity was 6/9 or better and those with 6/12 or worse, $\chi^2=26\cdot34$, $p<0\cdot001$. If a dividing line is drawn between 6/12 or better and 6/18 or worse, $\chi^2=11\cdot97$, $p<0\cdot001$. Similarly, if a line is drawn between 6/18 or better and 6/24 or worse, $\chi^2=9\cdot45$, $p<0\cdot01$.

### POSSIBLE EFFECT ON EMMETROPISATION OF WEARING HYPERMETROPIC SPECTACLES FROM THE AGE OF 6 MONTHS

Similar information was available in the case of 144 children who were randomly allocated treatment with spectacles from the age of 6 months, and this permits observations on the question of whether treatment with spectacles caused these infants to remain hypermetropic. A valid comparison of the effect of *prescribing* spectacles on emmetropisation can be made when the fate of all those drawn for treatment is compared with those drawn for no treatment. When this is done (Table 3), there is a suggestion that the prescription of spectacles might have impeded emmetropisation, but the difference is not statistically significant ($p>0\cdot05$). A proportion of the children allocated spectacles did not wear them. At each follow-up attendance an assessment of compliance with treatment was attempted.[9] This group can therefore be subdivided into those who seemed to be wearing their glasses consistently (T+), and those who were obviously not doing so (T±). If the sub-group who consistently wore their glasses (T+) are compared with those who wore their glasses some of the time or not at all (T±), and with those drawn for no treatment, the numbers of children who reduced their hypermetropia or did not do so are as follows (Table 4). The sub-group T+ were significantly less likely to have reduced their meridional hypermetropia to less than +3·50 D than either the sub-group who wore their glasses inconsistently (T±) ($\chi^2=9\cdot96$, $p<0\cdot01$), or those originally drawn for no treatment ($\chi^2=10\cdot57$, $p<0\cdot01$).

*Table 1 Emmetropisation and squint*

| | *No squint* | *Squint* |
|---|---|---|
| Emmetropisation had not occurred | 16 | 29 |
| Emmetropisation had occurred | 88 | 10 |

$\chi^2=43\cdot05$, df=1, $p<0\cdot001$

*Table 2 Emmetropisation and the last known visual acuity*

| | *6/6 and 6/9* | *6/12* | *6/18* | *6/24 or worse* |
|---|---|---|---|---|
| Emmetropisation had not occurred | 23 | 9 | 5 | 8 |
| Emmetropisation had occurred by 3½ | 89 | 3 | 4 | 2 |

$\chi^2=30\cdot05$, df=3, $p<0\cdot001$.

*Table 3 Emmetropisation and the prescription of spectacles from age 6 months*

| | *Children allocated spectacles* | *No treatment allocated* |
|---|---|---|
| Emmetropisation had not occurred | 60 | 45 |
| Emmetropisation had occurred | 84 | 98 |

$\chi^2=2\cdot79$, df=1, $p>0\cdot05$.

Most of those children whose meridional hypermetropia became less than +3·50 D had achieved this by the age of 1 year. 82% of those drawn for no treatment, and who were considered to have corrected their hypermetropia, had done so by 1 year. The corresponding figure for those drawn for treatment but whose compliance was judged to be poor (T±) was 63%, and for those who consistently wore their glasses (T+) was 47%. Thus delay in emmetropisation was apparent by the age of 1 year.

*Table 4 Emmetropisation and the consistent wearing of spectacles*

| | *Subgroup T+* | *Subgroup T±* | *Children drawn for no treatment* |
|---|---|---|---|
| Emmetropisation had not occurred | 39 | 21 | 45 |
| Emmetropisation had occurred | 31 | 53 | 98 |

*Table 5 Initial meridional hypermetropia of children in each of the three subgroups*

| *Meridional hypermetropia at 6 months* | *Number of children in subgroup (T+)* | *Number of children in subgroup (T±)* | *Number of children drawn for no treatment* |
|---|---|---|---|
| +4·00 | 27 | 33 | 74 |
| +4·50 | 13 | 19 | 28 |
| +5·00 | 14 | 8 | 20 |
| +5·50 | 8 | 7 | 7 |
| +6·00 | 5 | 6 | 9 |
| +6·50 | 0 | 1 | 3 |
| +7·00 or more | 3 | 0 | 2 |

One might reasonably guess that those infants who were initially most hypermetropic would be the ones least likely to correct their hypermetropia. Such children might also be more likely to derive benefit from wearing glasses, wear them consistently, and therefore fall into the T+ subgroup. If this had happened, it could have biased the findings towards our observation that consistent wearing of spectacles appears to have impeded emmetropisation. This is unlikely to have been the case, however, because there was not an obvious preponderance of infants with the higher levels of meridional hypermetropia among the T+ subgroup (Table 5).

## Discussion

The classical view that all infants are hypermetropic[10] and that those who remain hypermetropic are particularly likely to present with accommodative esotropia has never been demonstrated. All infants are not 'abnormally' hypermetropic.[11] Only about 10% of those that we screened at 6 months were sufficiently long-sighted to be included in our trial of preventive treatment. However, if the criteria, which we have chosen arbitrarily, to decide whether emmetropisation had or had not occurred are accepted, there is confirmation that in the case of 'abnormally' hypermetropic infants failure to reduce their hypermetropia is associated with subsequent identification of squint (Table 1, $p<0\cdot001$). We have independently made the same observations as Aurell and Norrsell.[12] Our sample of children, however, was not restricted to those with a family history of squint/amblyopia.

We think that emmetropisation was most likely to have occurred before the age of 1 year, though the process did continue after then. We found that those children whose meridional hypermetropia was not reduced to less than +3·50 D were significantly more likely (Table 2, $p<0\cdot001$) to end up with worse visual acuity than those whose hypermetropia was reduced to less than +3·50 D. The association between emmetropisation on the one hand and a lower incidence of squint and better visual acuity on the other hand was statistically more significant than any improvement that could be shown following the prescription and wearing of glasses in the same sample of children.[9] The promotion of emmetropisation, if that were possible, might be preferable to enthusiastic prescription of spectacles as a method of preventing squint and improving visual acuity. Basic information about emmetropisation in animals is being reported, but we need to know what factors could affect it in man.

Our observations about the effect of spectacles on emmetropisation in this sample of children may give a clue to this. The prescription of glasses did not significantly impede emmetropisation (Table 3), but, when those children drawn to wear spectacles were separated into two subgroups, those who were judged to have consistently worn their glasses (T+) were significantly less likely to have reduced their hypermetropia than either those who probably or certainly did not wear glasses consistently (T±) (Table 4, $p<0\cdot01$) or those who were randomly allocated no treatment (Table 4, $p<0\cdot01$). Although judgment on whether glasses had been worn consistently was made before these figures were worked out, those regarded as having consistently worn glasses might be considered to be a self-selected group. Nevertheless, these findings support Lyle's speculation[10] that spectacle correction of hypermetropia might impede emmetropisation. They also confirm the observations of Dobson *et al*,[13] who have reported that 10 infants, prescribed spectacles because they had convergent squint, showed a significantly smaller decrease in hypermetropia than a group of 30 non-strabismic infants with equivalent hypermetropia who were not prescribed spectacles.

So far as we are aware there are only two other reports of the opposite of emmetropisation in children – that is, increasing hypermetropia at some time between birth and the age of 7 years. Both studies were conducted on patients, not random samples of the population. Over two-thirds of Brown's subjects[14] had squint, and most of those probably wore hypermetropic spectacles. Many of Slataper's subjects were probably treated for squint also.[15] Some children being treated for accommodative esotropia do become more hypermetropic,[16] and this change could be influenced by the wearing of hypermetropic spectacles. The mechanism of such an influence is problematical but could include a reduction in the need for accommodation, and accommodation in its turn might be involved in the reduction of hypermetropia. As a corollary to this, some believe that excess accommodation is one factor contributing to the increase in myopia at or after puberty.

We thank Mrs L Neale for many hours of secretarial and administrative work

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# Comparison of retrobulbar and periocular injections of lignocaine by computerised tomography

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## Abstract

**Ten patients undergoing cataract surgery were given a local anaesthetic with lignocaine solution which was mixed with iohexol contrast medium. The location of the needle and the substance injected was determined by computerised tomography following retrobulbar or periocular anaesthesia. The retrobulbarly inserted needles were within the muscle cone, directed towards the optic foramen. The periocular needles were outside the muscle cone, tangentially along the orbital floor or pointing slightly upwards. After the retrobulbar injection the contrast medium was seen within the cone immediately after the injection and outside the cone as early as 3 minutes after the injection. With the periocular technique, however, diffusion of the anaesthetic in the opposite direction (that is, into the muscle cone) was rapid. The contrast medium was identified inside the muscle cone 2 minutes after the injection. Compression with an intraocular pressure reduction device after both of these techniques prevented exophthalmos. It is concluded that retrobulbar-like anaesthesia can also be induced by an appropriate periocular technique.**

The retrobulbar injection of lignocaine has long been used to provide analgesia and akinesia in ocular surgery. However, it carries rare but undoubted risks, for example, blindness, optic nerve penetration, scleral perforation, retrobulbar haemorrhage, meningeal irritation, and respiratory arrest.[1] According to Unsöld *et al*[2] most of the complications arise from direct trauma to the orbital structures. They studied the location of the needle in a cadaver orbit using computerised tomography (CT) after retrobulbar injection and suggested an alternative position of gaze (primary gaze or slightly downward and outward). Apparently the traditional upward and inward gaze rotates the essential structures into the path of the needle.[2] Katsev *et al*[3] studied the path length of the retrobulbar needle and recommended that needles should be less than 31 mm behind the orbital rim for both retro- and peribulbar anaesthesia. Recently, in a modification of the retrobulbar technique termed 'conal anaesthesia' the retrobulbar space is approached with a curved rather than a straight needle.[4]

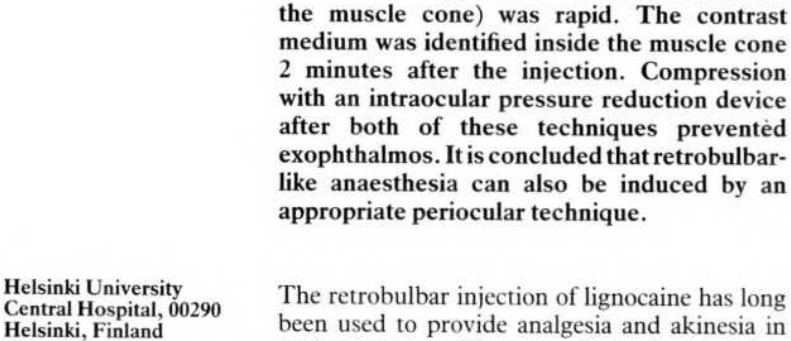

*Figure 1 The needle lies in the retrobulbar space close to the optic nerve, verified by density measurements and neighbouring levels. Contrast medium is within the muscle cone at 3 min after the injection. 1=contrast medium, 2=medial rectus muscle, 3=needle, 4=optic nerve.*

In periocular anaesthesia the risk of direct injury of the delicate neural and vascular structures of the orbit is reduced because the needle lies outside the muscle cone.[1]

The aim of the present study was to examine the exact location of the needle together with the spread of the local anaesthetic solution in retrobulbar and periocular anaesthesia. In addition, the effect of ocular compression on postinjection exophthalmos was studied.

## Patients and methods

Ten patients scheduled for elective cataract extraction gave informed consent to the study, which was approved by the Ethics Committee of the Department of Ophthalmology of Helsinki University Central Hospital. The lignocaine was administered by one of two routes: periocularly in six patients and retrobulbarly in four patients. Details of the patients are given in Tables 1 and 2.

Periocular anaesthesia was by a single inferolateral injection. The sharp needle (25 g, 25 mm, Terumo, Belgium) was introduced through the skin immediately above the orbital rim along the orbital floor, care being taken to maintain the needle outside the muscle cone.

The retrobulbar anaesthesia technique was with a semisharp 35 mm needle (2R2, Luer Lock). An intraocular pressure reducer device (Autopressor, Storz, Heidelberg, Germany) was applied for 10 minutes at a pressure setting of 25 mm Hg in two patients of the periocular group and one patient of the retrobulbar group. 20 ml of 2% lignocaine solution was mixed with 0·5 ml of water-soluble contrast medium iohexol (Omnipaque, 360 mg iodine/ml, Nycomed, Norway). The volume of mixture injected by the periocular method was 4 ml and by the retrobulbar method 3 ml.

The position of the needle was examined in two patients in each of the two techniques. The injected mixture of lignocaine and contrast medium was inspected with the aid of CT (Somatom DRH, Siemens, Germany; the scanning parameters: time 7 s, 125 kV, slice thickness 2 mm). Scanning was begun immediately after the injections and was continued for 25 to 30 minutes.

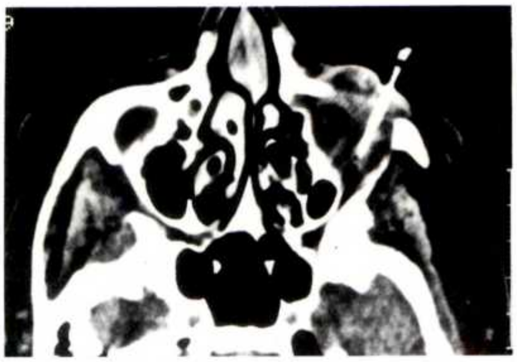

*Figure 2 The periocularly inserted needle is seen outside the muscle cone tangentially along the orbital floor beneath the inferior rectus muscle. The slice is taken beneath the level of the globe.*

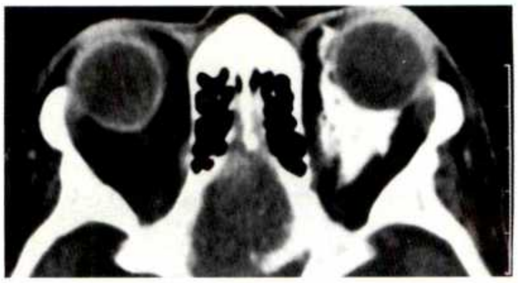

*Figure 4 In addition to the retrobulbar space contrast medium is seen superiorly outside the muscle cone 3 min after the retrobulbar injection.*

## Results

Both needles following the retrobular injections were found to be within the muscle cone. In one of the patients the needle was in close proximity to the optic nerve (Fig 1). On the other hand, when the periocular technique was used, one needle was seen tangentially along the orbital floor (Fig 2) under the inferior rectus muscle, while the second needle was orientated slightly upwards outside the muscle cone.

In the retrobulbar injections the contrast medium was seen within the muscle cone immediately after the onset of scanning (Fig 3). In all the patients in whom the retrobulbar technique was applied it was seen outside the muscle cone from 3 to 8 min (Table 1, Figs 4, 5). The contrast medium remained both within and outside the muscle cone during the 25-30 minutes (Fig 6). In all patients the contrast medium surrounded the optic nerve along its full length within the orbit.

As regards the periocular injections, the contrast medium was detectable outside the muscle cone in all patients from the start of the scanning. It was detectable above the superior rectus muscle within 1·5 to 3 minutes (Fig 7). In all patients, it was also evident within the muscle cone (Fig 8) occurring first there at 2–6 minutes after the injection (Table 2). Later on contrast medium was detected in the orbit so long as scanning was continued (Figs 9, 10). The contrast medium surrounded the optic nerve along its entire route in the orbit in four patients and for a distance of 1 cm retrobulbarly in two patients.

Exophthalmos (of respectively 3, 4, and 5 mm) occurred after the retrobulbar injection in the three patients in whom no compression was used. However, in the patient treated with compression there was no apparent exophthalmos. As regards the periocular injections, in the four patients not treated with compression no exophthalmos was detected in two, while in the remaining two patients an exophthalmos of 3 mm and 5 mm respectively occurred. In the two patients in whom compression was used following the periocular injections no exophthalmos was seen.

## Discussion

In the two patients in whom the retrobulbar technique was used both needles were directed obliquely towards the optic foramen within the muscle cone. The position of the needle in close proximity to the optic nerve verifies the potential risk of penetration of this nerve or the injection of the anaesthetic solution into the subarachnoid

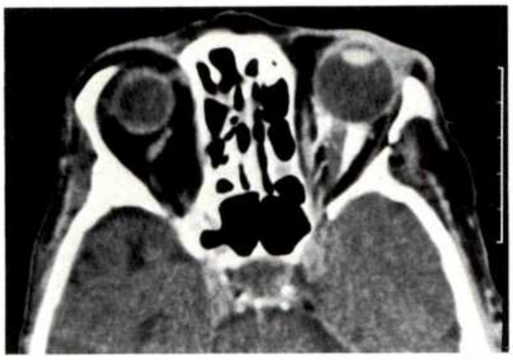

*Figure 3 Retrobulbar space is filled with contrast medium 2·5 min following the retrobulbar injection.*

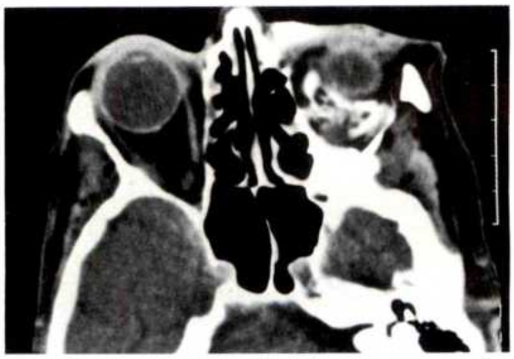

*Figure 5 Contrast medium fills the intra- and extraconal spaces 6 min after the retrobulbar injection.*

*Table 1 Demographic data, use of ocular compression, and presence of the needle during scanning of patients in retrobulbar group. The time of detecting the contrast medium intra- or extraconally, and the occurrence of exophthalmos, are given*

| | | | | | *Contrast medium* | | |
|---|---|---|---|---|---|---|---|
| *Patient* | *Sex* | *Age (yr)* | *Ocular compression* | *Needle localised* | *Intraconally (min after injection)* | *Extraconally* | *Exophthalmos (mm)* |
| 1 | F | 75 | – | + | 3 | 8 | 5 |
| 2 | F | 70 | – | + | 3·5 | 3 | 3 |
| 3 | F | 81 | + | – | 1·5 | 6 | 0 |
| 4 | F | 61 | – | – | 3 | 3 | 4 |

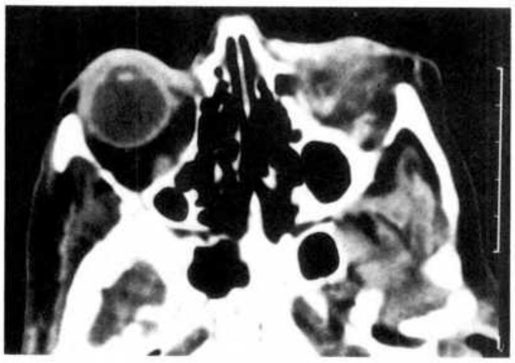
*Figure 6  At 24 min after the retrobulbar injection contrast medium is still obvious in the orbit.*

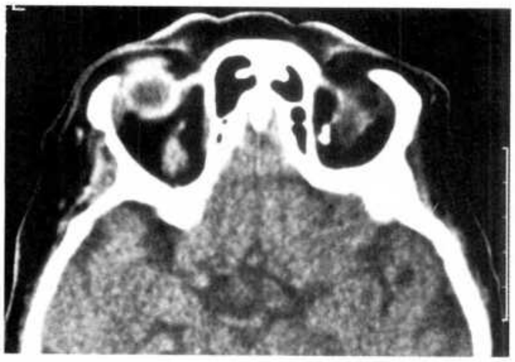
*Figure 7  Contrast medium is seen extraconally above the superior rectus muscle 3 min after the inferolateral periocular injection.*

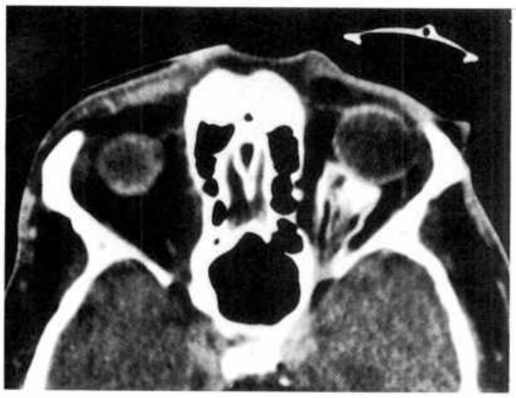
*Figure 8  At 4 min after the periocular injection contrast medium is both intra- and extraconaly.*

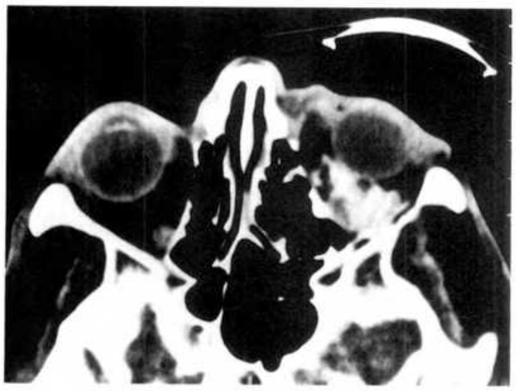
*Figure 9  At 8 min after the periocular injection contrast medium fills the orbit.*

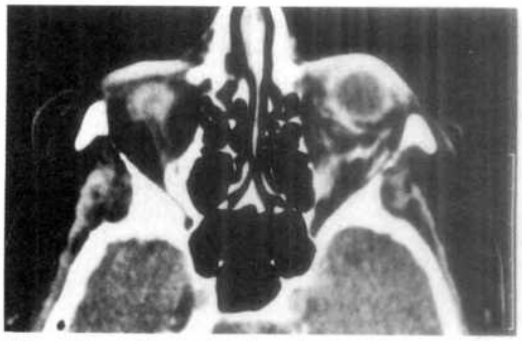
*Figure 10  At 24 min after the periocular injection contrast media is both within and outside the muscle cone.*

space. On the other hand, the two periocular needles were safely outside the cone, far from important structures. The different placement of the needle was also noticed clinically: immediately after the injection, the retrobulbar needle, which had pierced the intermuscular septum, moved with the globe, while the periocular needle did not.

The contrast medium and anaesthetic diffused within a few minutes; there was similar localisation of the contrast medium by both techniques irrespective of the different position of the needle. The rapid diffusion of lignocaine is in accord with a recent finding that akinesia in periocular anaesthesia is usually achieved within some 4 minutes.[5] Anatomically in the anterior orbit the fascial sheaths of the rectus muscles produce confluent intermuscular fibrous septa, but posterior to the globe the intermuscular fibrous septa are interrupted.[6] The fact that there was no difference in the localisation of the injected substance at 2 min supports this theory.

In an earlier study akinesia in periocular akinesia was found not to be dependent on ocular compression.[7] The beneficial effect of ocular compression on exophthalmos was noted after both the retrobulbar and the periocular techniques. The absence of exophthalmos after the periocular injection in the patients without compression might be due to the immediate localisation of the injectate round the eye rather than behind the eye, as in retrobulbar anaesthesia.

Computerised tomography revealed that, irrespective of the technique and therefore of the location of the needle, localisation of lignocaine together with the contrast medium was similar by both methods in a few minutes. As both the contrast media and lignocaine are water soluble, one might expect that at least at the onset of the scanning the flow of the agents would be similar. Periocular anaesthesia has been reported to be as effective as retrobulbar anaesthesia.[8] In the

*Table 2  Demographic data, use of ocular compression, and presence of the needle during scanning of patients in periocular group. The time of detecting the contrast medium intra- or extraconally, and the occurrence of exophthalmos, are given*

| | | | | | *Contrast medium* | | |
|---|---|---|---|---|---|---|---|
| *Patient* | *Sex* | *Age (yr)* | *Ocular compression* | *Needle localised* | *Intraconally (min after injection)* | *Extraconally* | *Exophthalmos (mm)* |
| 1 | F | 77 | – | – | 6 | 6 | 3 |
| 2 | F | 83 | – | – | 2 | 2 | 5 |
| 3 | F | 70 | – | + | 4 | 3 | 0 |
| 4 | M | 88 | + | – | 5 | 5 | 0 |
| 5 | M | 72 | – | + | 4 | 1 | 0 |
| 6 | M | 39 | + | – | 3 | 2 | 0 |

present study the location of the anaesthetic was similar by both methods as early as 3–4 min after the injection. The position of the needle, at least in our hands, seems to be safer in the periocular rather than in the retrobulbar method. Confirming earlier studies, this study shows that the periocular technique can be recommended as an alternative anaesthetic technique for ophthalmic surgery.

This study was supported by the Eye Foundation and the Paulo Foundation, Helsinki, Finland.

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# Experimental *Acanthamoeba* keratitis: II. Immunohistochemical evaluation

D F P Larkin, D L Easty

**Abstract**

**In a Wistar rat experimental model of *Acanthamoeba* keratitis immunohistochemical techniques were used to analyse the host cellular response. The inflammatory cell profile was observed to change at intervals. In tissue sections the cellular response consisted of neutrophils on the first day but predominantly macrophages on the following days. Some T lymphocytes but no B lymphocytes were observed.**

The free-living amoeba *Acanthamoeba* causes infection at two distinct sites. It was first demonstrated to cause granulomatous encephalitis: this occurs in chronically ill or immunocompromised patients and is usually fatal.[1] Infection of the cornea later became recognised and is now more frequently diagnosed. *Acanthamoeba* may be cultured from corneal scrape or biopsy specimens, or may be demonstrated in tissue sections. The amoeba causes painful blinding keratitis and, in contrast to encephalitis, is usually seen in healthy people who wear contact lenses.[2,3] *Acanthamoeba* keratitis typically has a chronic progressive course, with stromal infiltration and frequent failures of medical and surgical treatment.[4]

The reasons why this organism of low virulence causes progressive ocular infection in normal hosts, and why keratitis often responds poorly to agents shown in vitro to be effective against the cultured isolate are unknown. Study of the host immune response to *Acanthamoeba* infection is very limited because only corneal transplantation specimens are available for study; such patients have in most cases been intensively treated with anti-inflammatory agents prior to surgery. Consequently, available reports[4-6] describe the late stages of the disease, probably modified by drug therapy.

Most pathological reports describe an acute inflammatory cell infiltrate in the stroma, with in some cases a sparse added lymphocyte component.[4,5] The report on two patients by Mathers and colleagues was the first to define by immunohistochemical methods the inflammatory response in *Acanthamoeba* keratitis.[6] They found that the inflammatory cell population comprised 80–100% neutrophils and macrophages near the site of active corneal ulceration.

The immune response of the host is probably important in development of this infection, and an analysis of the inflammatory cell types within the cornea subsequent to infection provides further understanding of the mechanisms of disease. A rat model of experimental *Acanthamoeba* keratitis has been established in which the infection is induced by intrastromal injection of the cyst form of *Acanthamoeba*.[7] Untreated tissue can be studied pathologically at specified intervals after disease induction. Conventional histological techniques and immunohistochemical staining with monoclonal antibodies against cell markers have been used to characterise the constituent cell types.

## Materials and methods

### ACANTHAMOEBA INOCULATION AND CLINICAL EXAMINATION

The detailed procedure for induction of experimental keratitis has been previously reported.[7] Briefly, an axenic cyst suspension of a human keratitis isolate (*A polyphaga*, strain Shi) was prepared at a concentration of $1\times10^6$/ml in Page's amoeba saline. 1 μl of this suspension was inoculated by intrastromal injection into the right cornea of outbred 125 g male Wistar rats under general anaesthesia. The concentration of this suspension was predetermined as the dose necessary to induce reproducible clinical keratitis.

On days 1, 3, 5, 7, and weekly thereafter until 12 weeks following inoculation the rats were examined under general anaesthesia by slit-lamp. Corneal inflammation was graded on a scale of 0–3 for opacity (grade 0 being normal and grade 3 indicating dense corneal opacity), and the mean score for all infected corneas at each time interval was calculated. All procedures described conformed to the ARVO resolution on the Use of Animals in Research.

### PREPARATION OF WAX SECTIONS

Two rats were killed by intraperitoneal injection of 60 mg pentobarbitone on days 1, 3, 7, 14, 21, 42, and 84 days after inoculation. The right eye was enucleated; the cornea was dissected and halved. One half was fixed for 24 h in neutral buffered formaldehyde, embedded in wax, and 6 μm sections cut with a microtome. Sections were stained, as previously described, with haematoxylin and eosin or rabbit anti-*Acanthamoeba* antibody (staining trophozoite or cyst forms brown).[7]

### PREPARATION OF FROZEN SECTIONS

Hemicorneas from eyes enucleated as described above were mounted in embedding compound (Tissue-Tek OCT, Miles Scientific, Naperville, Il) and snap-frozen in liquid nitrogen. Sections of 6 μm thickness were cut with a cryostat (2800 Frigocut-E, Reichert-Jung) at −30°C. Sections were mounted on polylysine-coated

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*Table 1 Monoclonal antibodies and incubations used in staining of corneas*

| *Antibody* | *Specificity* | *Dilution* | *Duration* | *Temperature* |
|---|---|---|---|---|
| ED2 | Macrophages[8] | 1·20,000 | 16 h | 4°C |
| MRC OX–19 | Pan-T cell[9] | 1.100 | 16 h | 4°C |
| MRC OX–33 | Pan-B cell[10] | 1 900 | 16 h | 4°C |
| MRC OX–39 | *Interleukin–2 receptor[11] | 1.250 | 30 min | 37°C |
| MRC OX–21 | †Human C3b inactivator[12] | 1·2 | — | — |

All monoclonal antibodies (Serotec Ltd, Oxford, England) were prepared from mouse hybridoma ascites fluid, except OX–21, which was prepared from tissue culture supernatant.
* Designating activated T-cells
† Negative control, reacts with human but not rat tissue.

glass slides, air dried, immersed in acetone for 5 seconds, and frozen at −85°C for storage.

### IMMUNOHISTOCHEMICAL STAINING OF FROZEN SECTIONS

Sections were stained by the peroxidase anti-peroxidase technique. Frozen sections were fixed in acetone for 10 min, air dried, and washed in distilled water for 30 min. Endogenous peroxidase activity was blocked by inoculation with 0·3% hydrogen peroxide for 30 min. After washing in phosphate-buffered saline (PBS), non-specific background staining was blocked by incubation with 1:5 normal rabbit serum in PBS for 30 min. Excess serum was blotted from sections, and mouse hybridoma monoclonal antibody was then added at specific dilutions, incubation times, and temperatures (Table 1). The sections were then washed and incubated with 1:50 secondary antibody (diluted with 1:10 normal rat serum) for 30 min at room temperature. Sections were again washed and incubated with 1:50 horseradish peroxidase anti-peroxidase (PAP) complex (diluted with 1:10 normal rat serum). After again washing with PBS, sections were incubated with a chromagen to identify antibody binding. For this purpose 3, 3′-diaminobenzidine (Sigma Chemical Co) was used, mixed with $H_2O_2$ in 0·1 M trometamol (Tris) buffer, giving a brown end product. After incubation for 7 minutes sections were washed in tap water for 5 minutes, counterstained with haematoxylin, and mounted.

Lymph node sections from normal Wistar rats, processed identically to the experimental sections, were used as positive controls. Lymph nodes contain a variety of inflammatory cell subtypes: thus node sections were moderately positive specimens, sensitive to variations in performance of the method. Experimental corneal sections for use as negative controls received, in place of primary antibody, an antibody which was known not to react with antigen in rat tissue. A monoclonal antibody against a human inflammatory product, MRC OX-21 (Serotec Ltd, Oxford, England), was used at dilution 1:2. This is a mouse monoclonal antibody against human C3b inactivator[12] and does not react with rat tissues.

### QUANTITATIVE ANALYSIS OF SECTIONS

The positively stained inflammatory cells or *Acanthamoeba* in the stroma of the central cornea were counted with a graticule at 400× magnification. Three adjoining fields in each of two corneas from rats killed at the same interval were evaluated and a mean count calculated.

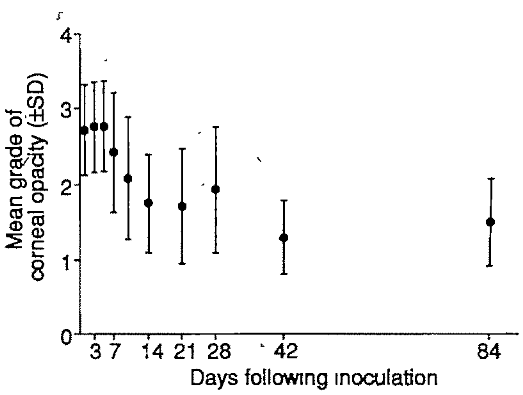

*Figure 1 Grade of corneal opacity at intervals after induction of infection. The mean grade of opacity of all infected corneas examined on that day is shown.*

## Results

### CLINICAL EVOLUTION OF KERATITIS

The inflammatory infiltration of the right cornea following *Acanthamoeba* inoculation as determined by slit-lamp examination is shown in Fig 1. Animals developed a stromal opacity which was granular in character. Corneal epithelial defects, vascularisation, perforation, and evidence of intraocular inflammation were not observed. Stromal opacity was maximal for the first seven days following inoculation and gradually declined after that time.

### IMMUNOPEROXIDASE STAINING OF ACANTHAMOEBA IN TISSUE SECTIONS

Numbers of staining amoebae are shown in Table 2. An increasing proportion of trophozoite *Acanthamoeba* was observed in sections at intervals following inoculation.

### CELLULAR COMPOSITION OF THE INFLAMMATORY INFILTRATE

Inflammatory cell types within the central stroma were identified by haematoxylin and eosin staining of neutrophils and by monoclonal antibody staining of surface antigens on macrophages, B cells, T cells, and activated T cells (Table 1). The relative number and proportions of inflammatory cells are shown in Table 3 and Figs 2A, B.

On day 1 neutrophils were the only inflammatory cell identified. A negligible number of other cell types staining with haematoxylin and eosin, which did not appear to be neutrophils, were not identified by staining with any of the monoclonal antibodies. On day three a similar total number of cells were seen but a proportion of these were macrophages.

*Table 2* Acanthamoeba *in central corneal stroma*

| *Day* | *Number of amoebae (mean)* | *SE* |
|---|---|---|
| 1 | 8·7 | 1 5 |
| 3 | 12·9 | 1·3 |
| 7 | 6 1 | 0·6 |
| 21 | 2·0 | 0·7 |
| 42 | 0 6 | 0·3 |
| 84 | 1·3 | 0·3 |

Trophozoite and cyst forms of *Acanthamoeba* were stained by immunoperoxidase technique using rabbit anti-*Acanthamoeba* antibody. SE=standard error

*Table 3 Inflammatory cell types in the central stroma of corneas infected by* Acanthamoeba

| Day | Neutrophils cells | % | ED2+ cells | % | OX–33+ cells | % | OX–19+ cells | % | OX–39+ cells | % | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 12<br>(1·0) | 100 | 0<br>— | — | 0<br>— | — | 0<br>— | — | 0<br>— | — | 12 |
| 3 | 10<br>(1·4) | 77 | 3<br>(0·8) | 23 | 0<br>— | — | 0<br>— | — | 0<br>— | — | 13 |
| 7 | 6<br>(0·5) | 15 | 24<br>(6·3) | 63 | 0<br>— | — | 8<br>(2·7) | 22 | 0<br>— | — | 38 |
| 14 | 6<br>(1·0) | 11 | 38<br>(1·3) | 68 | 1<br>— | 4 | 11<br>(2·3) | 20 | 5<br>(1·4) | 9 | 56 |
| 21 | 1<br>(0·6) | 3 | 20<br>(2 7) | 69 | 0<br>— | — | 8<br>(1·0) | 28 | 3<br>(0·8) | 10 | 29 |
| 42 | 1<br>(0·3) | 17 | 3<br>(0·5) | 50 | 0<br>— | — | 2<br>(0·4) | 33 | 1<br>(0·5) | 17 | 6 |
| 84 | 1<br>(0·1) | 14 | 4<br>(1·0) | 57 | 0<br>— | — | 2<br>(1 6) | 29 | 0<br>— | — | 7 |

Cell counts and percentage proportions of inflammatory cells in the central stroma of corneas infected by *Acanthamoeba*. Neutrophils were stained with haematoxylin and eosin. Other inflammatory cell types were stained with monoclonal antibodies ED2 (macrophages), OX–33 (B cells), OX–19 (T cells), and OX–39 (activated T cells). Positively stained cells were counted with a graticule at 400× magnification. Standard error of the cell count in three fields in each of two corneas is given in parentheses. The total cell number given excludes OX–39+ (activated T) cells, which are taken to be a subset of OX–19+ (pan T) cells

By day 7 macrophages had become the predominant cell type, constituting 63% of all cells. By this time neutrophils had sharply declined in absolute numbers and proportion (15%). T cells first appeared on day 7.

On day 14 the total cell count was highest. Macrophages continued to be the predominant cell type (Fig 3A). T cells constituted 20% of cells, and activated T cells were identified for the first time (Fig 3B). This indicates that the OX-19+ (pan-T) cells observed in earlier sections are probably not specifically directed against *Acanthamoeba* antigen.

On days 21 and 42 neutrophils continued to decline in numbers; macrophages continued to be the predominant constituent inflammatory cell; T cells and activated T cells continued to be observed in the same proportions. By day 42 the total number of inflammatory cells had markedly declined. On day 84 macrophages and T cells (OX-19+) persisted as the predominant cells in a sparse inflammatory infiltrate. Activated T lymphocytes (OX-39+) were no longer identified.

Almost no B lymphocytes were observed at any time, with only a solitary cell being stained, on day 14 (Fig 3C).

## Discussion

The extensive use of hybridoma technology has led to the development of new methods for the isolation of murine immunoglobulins from cell culture or ascites fluids.[13] Monoclonal antibodies reactive with cell surface antigens have become the primary tools for study of inflammatory cell, and particularly lymphocyte, heterogeneity. Surface markers have rarely been found to be absolutely specific for any one inflammatory cell type. However, the specificity for rat inflammatory cells reported for those antibodies used in this study has led to their wide use in immunocytochemistry. Antibodies specific for rat T cell individual subsets are not commercially available at the time of writing.

Immunohistochemical study of the immune response in *Acanthamoeba* keratitis is necessary because so many features of this infection suggest an unusual host response to the pathogen. These include poor response to amoebicidal drugs,[4] chronic clinical course, lack of corneal vascularisation in human and experimental disease,[6,7] and lack of lymphocyte response in human pathological studies.[5,6]

In experimental *Acanthamoeba* keratitis we have identified a dynamic process in which the inflammatory cell profile alters with time. The inflammatory cell population was observed to be entirely neutrophil on day 1, with macrophages becoming the predominant cell type by day 7. T cells, including activated T cells, were constituents of the immune response after the first week; B cells were conspicuously absent. The numerical increase in amoebae seen at day 3 may be due to excystment and trophozoite multiplication. Decline after this time probably reflects destruction by inflammatory cells. While the clinical severity of keratitis was maximal in the first week, and the number of *Acanthamoeba* in tissue sections appeared maximal at day 3, the number of inflammatory cells was highest at day 14. These findings may indicate that amoebic destruction by the rat inflammatory response was maximal at around day 14. Destruction of amoebae was observed in sections at various time points but not quantified.

Immunohistochemical data from our study form an interesting contrast with those from two human corneal transplantation specimens reported by Mathers and colleagues.[6] These authors found that 80% to 100% of cells near the site of corneal ulceration were neutrophils or macrophages; no B or T cells were found in one cornea, and T cells constituting 10% with no B cells in the other. In both human and animal disease the reason for the absence of B cells in the inflammatory cell infiltrate is uncertain. It is unlikely that lack of corneal vascularisation explains the absence of B cells. In a model of experimental keratitis in the rat induced by

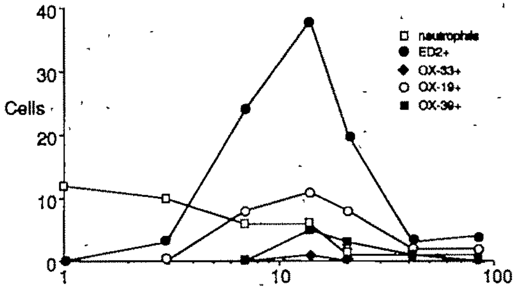

*Figure 2A Differential inflammatory cell counts in infected corneas at intervals after inoculation of* Acanthamoeba. *Horizontal axis is log scale.*

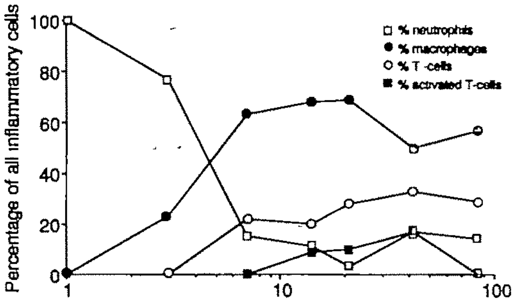

*Figure 2B Differential inflammatory cell percentage proportions. Horizontal axis is log scale.*

*Figure 3 Frozen sections of rat central cornea 14 days after inoculation with* Acanthamoeba. *The sections were stained with monoclonal antibody: the brown colour indicates positive staining and the light purple colour is haematoxylin counterstain.* (A) *ED2 staining of a number of cells (small arrows) around* Acanthamoeba *cysts (large arrow) (×270).* (B) *MRC OX–39 staining of activated T cells (arrow) in anterior stroma (×170).* (C) *A solitary MRC OX–33 staining B cell (arrow) in deep stroma (×170). This was the only cell observed in any section which stained with this antibody.*

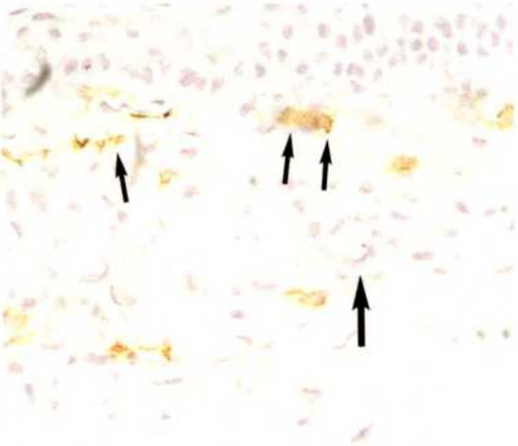

Figure 3A

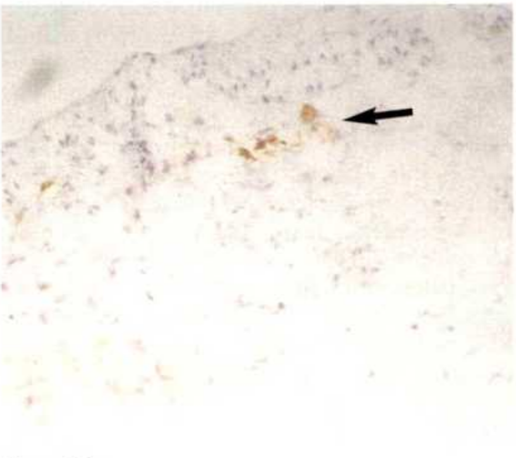

Figure 3B

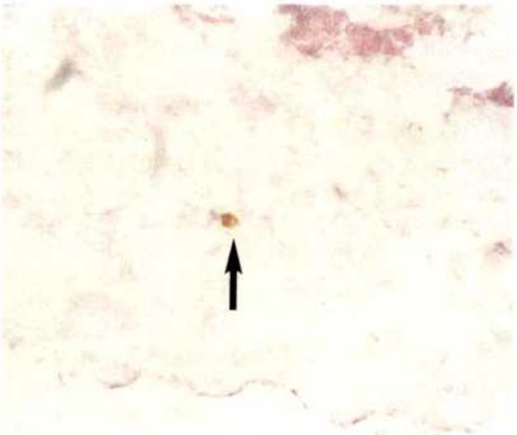

Figure 3C

intrastromal injection of heat inactivated rabbit serum Verhagen and colleagues observed corneal vascularisation but no B lymphocytes in the inflammatory infiltrate.[14] In experimental *Acanthamoeba* infection it is, however, possible that there is systemic production of antibody without plasma cell or B cell infiltration into cornea. In this study we did not examine the serum for a measurable antibody response, which has been found in human infection.[15]

Immunological tolerance, the acquisition of non-reactivity towards particular antigens, may independently involve B and T cells and might explain the absence of B lymphocytes in the cornea. It might be that B cells are immature in the 6–8-week old rat, and that B cells encountering antigen for the first time become tolerant. Tolerance might also be mediated by soluble factors from suppressor T cells, and antigen-specific suppressor T cell-induced tolerance has been observed in mice.[16] Finally, as normal B cell responses to T-dependent antigens require help of specific T cells, reduced production of B cell maturation lymphokine IL-4 by the $H_1$ category of helper T cells might cause functional B cell deletion.

Further studies are necessary to characterise more comprehensively the immune response to *Acanthamoeba*. We plan to survey infected rat cornea for T cell subsets and class II major histocompatibility complex (MHC) antigens which would indicate local presentation of antigen. It would also be informative to extend immunohistochemical study to the limbus and local lymph nodes.

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# Childhood blindness in the Republic of Ireland: a national survey

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## Abstract

**We completed a national study of blindness in children under 16. Approximately 80% of the blind children (that is, with vision of 3/60 or less) in the Republic of Ireland (172 children) were seen, 93 males and 79 females. The survey was carried out between July 1989 and June 1990. It is the first such study to be carried out. Ninety seven (56%) children had lesions due to factors acting before the perinatal period. Of these, 28 (16% of the total number surveyed) had lesions due to genetic causes; 69 (40%) had lesions due to factors operating in the prenatal period other than genetic factors. Forty six (27%) had lesions due to factors acting in the perinatal period. Twenty two (13%) had lesions due to factors acting in childhood. (4% could not be categorised in this way). The commonest single primary diagnoses were birth asphyxia in 19 (11%) cases and retinopathy of prematurity in 19 (11%) cases.**

This report outlines the major findings of a national survey of blind children in the Republic of Ireland. A survey carried out in Northern Ireland in 1976[1] found 142 patients under 21 years blind by World Health Organisation (WHO) standards – that is, visual acuity of 3/60 or less.[2] This represents about 0·02% of the under 21 population at that time. The current population of the Republic aged under 16 is 1 094 932 (at the last census in 1986). These figures would suggest that there are about 220 blind children under 16 in the Republic at present. Information on childhood blindness was not available in the Republic before this survey.

*Table 1 Ophthalmic diagnoses by category*

| | | | |
|---|---|---|---|
| *Category chromosomal/genetic: 28 cases* | | | |
| Leber's amaurosis | 3 | Anophthalmos | 2 |
| Cortical blindness | 3 | Optic atrophy | 2 |
| Optic nerve hypoplasia | 3 | Rothmund-Thompson | 2 |
| Albinism | 3 | Microphthalmos/coloboma | 2 |
| Cataract | 3 | Buphthalmos | 1 |
| Leber's optic atrophy | 2 | Usher's syndrome | 1 |
| Retinitis pigmentosa | 2 | Stargardt's syndrome | 1 |
| Metabolic retinopathy | 2 | | |
| *Category· prenatal· 69 cases* | | | |
| Optic nerve hypoplasia | 25 | Congenital toxoplasmosis | 2 |
| Optic atrophy | 21 | Peters's anomaly | 2 |
| Cortical blindness | 10 | Buphthalmos | 2 |
| Pigmentary retinopathy | 6 | Corneal dystrophy | 1 |
| Microphthalmos/coloboma | 5 | Motor nystagmus | 1 |
| Congenital rubella | 5 | Bilateral amblyopia | 1 |
| Cararact | 5 | Uveitis (? cause) | 1 |
| Anophthalmos | 4 | | |
| *Category: perinatal. 46 cases* | | | |
| Retinopathy of prematurity | 19 | Cortical blindness | 11 |
| Optic atrophy | 14 | Optic nerve hypoplasia | 9 |
| *Category· childhood. 22 cases* | | | |
| Optic atrophy | 9 | Uveitus (? cause) | 1 |
| Retinoblastoma | 8 | Retinal detachment | 1 |
| Cortical blindness | 3 | | |
| *Category· unassigned. 7 cases* | | | |
| Tractional retinal detachment | | | 2 |
| Optic atrophy ?cause | | | 2 |
| Optic nerve hypoplasia with hormone deficiencies | | | 1 |
| ? Viral retinal pigment epitheliitis | | | 1 |
| Isolated microphthalmos | | | 1 |

We set out to identify and record all blind children in the Republic of Ireland, and to institute a national live register of blind children.

## Materials and methods

### SOURCES OF REFERRAL

A national survey of blind children under 16 years old on 1 July 1989 (that is, born on or after 2 July 1973) whose best corrected vision was 3/60 or worse in their better eye was carried out. Patients were sought by several methods. All consultant ophthalmologists were circularised. The schools for blind and physically handicapped, the mental handicap institutions, the social service and educational bodies responsible for care of the blind were contacted nationwide to refer suitable patients and also asked for any records of patients known to them who fitted the criteria. They provided comprehensive lists of such cases.

### EXAMINATION OF PATIENTS

We examined all the patients. A history was taken when possible from a parent or a responsible adult. This included a family history, a history of the pregnancy, birth, and early postnatal period, and any relevant previous medical and ophthalmic history. Confirmatory medical data were sought when necessary from the relevant medical institutions.

The best corrected visual acuity was measured by the appropriate method for age, ability to co-operate, and level of intelligence. When possible this was by Snellen chart for distant vision. When the child was too young for the use of subjective tests of visual acuity, an assessment of the ability to fixate was made. Patients with central unsteady, unmaintained fixation or worse were deemed eligible for registration. When possible with the more co-operative patients and when the patients were able to attend the Children's Hospital more accurate measurements were made by Forced Choice Preferential Looking techniques. Ability to distinguish a pattern of 1·5 cycles/degree or less at 38 cm (that is, an approximate Snellen equivalent of 3/60 or less) was taken as the criterion for inclusion in the study. Electrophysiological examinations were carried out when necessary.

A full ophthalmic examination was undertaken in every case. A systemic examination was carried out by a paediatrician at the Children's Hospital if it was required to establish a diagnosis. Laboratory investigations were also carried out if necessary for a diagnosis. *X* rays, CT scanning, nuclear magnetic resonance (NMR) imaging, and ultrasound examination were undertaken for the same purpose.

All the relevant data were collected on data sheets and put in a computer database for future retrieval.

## Results

A total of 172 blind children were seen. There were 93 males and 79 females, a ratio of 1·18:1. Seventy nine (46%) of the children registered were aged under 5, 39 (23%) were aged 5 to 10 years inclusive, and 54 (31%) were 11 or over but under 16 on 1 July 1989.

An ophthalmic diagnosis was recorded for all the children seen. A systemic diagnosis was also recorded in 112 cases (65%). The diagnosis was assigned to a category, genetic or chromosomal, prenatal, perinatal, or childhood depending on the aetiology. A complete list of diagnoses by category is given in Table 1. Many children had several related diagnoses.

### CHROMOSOMAL OR GENETIC

Twenty eight children (16%) had diagnoses that fell into this group. Leber's amaurosis, albinism, and cortical blindness associated with genetic or chromosomal disorders were the most frequent diagnoses, with three cases each. The lesions causing cortical blindness were an extra chromosome 15, Pelizaeus-Merzbacher disease, and a peroxisomal disorder. Two cases of Rothmund-Thompson syndrome were discovered. Two cases of retinopathy associated with metabolic disorders were seen, one with Tay-Sachs disease and the other with a peroxisomal disorder. One case of Patau's syndrome with bilateral anophthalmos was seen. A deletion of the short arm of chromosome 11 was associated with aniridia, corneal opacity, and cataract in one child. Dicarboxylic aciduria was associated with optic atrophy in another.

In three families a history of parental consanguinity was obtained (1·74%). In two of these the parents were first cousins and in the third family second cousins. The diagnoses were bilateral anophthalmos and optic nerve hypoplasia in the first two cases, and optic atrophy in a background of hydrocephalus from aqueduct stenosis in the third.

### PRENATAL

These were cases with lesions occurring before the perinatal period that could not be classified as chromosomal or genetic: 69 cases (40%) fell into this category. The most frequent findings here were optic nerve hypoplasia in 25 cases and optic atrophy in 21. Cortical blindness was diagnosed in 10 cases. Many of the latter two diseases were secondary to systemic abnormalities such as hydrocephalus or metabolic disorders (many of which were not fully elucidated at the time of the study) and were associated in the same patient. Optic nerve hypoplasia was associated with absent corpus callosum, fetal alcohol syndrome, twin-to-twin transfusion, spina bifida, and septo-optic dysplasia. Rubella syndrome was diagnosed in five, the youngest being 11 years old. A further five each had colobomata or non-hereditary cataract. One child with colobomata was thought to have Goltz syndrome, but because the evidence was inconclusive she was categorised as having a coloboma of prenatal cause rather than hereditary (Goltz syndrome is thought to have an X-linked pattern of inheritance).

### PERINATAL

A total of 46 (27%) cases were in this group. Nineteen cases of retinopathy of prematurity were seen, 14 of optic atrophy, and 11 of cortical blindness. The latter two diseases were frequently seen together in the same patient and caused by hypoxic ischaemia from birth trauma. Nineteen cases of hypoxic ischaemic damage causing blindness were seen. In nine further cases there was documented birth trauma, but examination revealed optic nerve hypoplasia associated with the primary cause of blindness (namely, cortical damage or optic atrophy usually), implying some underlying prenatal abnormality.

### CHILDHOOD

Twenty two patients (13%) had lesions occurring after the perinatal period. Eight of these had bilateral retinoblastoma, for which seven were treated by bilateral enucleation. The eighth received radiotherapy to the second eye, which became blind subsequently. It is likely that some of these bilateral cases have a genetic aetiology. However, none had affected parents, siblings, or more distant relatives. None were shown to have an abnormal karyotype. In the absence of firm evidence to suggest a genetic background they have been put in this category. Nine showed optic atrophy, six following infective encephalopathies (two of whom also had cortical vision defects) and three secondary to intracranial tumours. One other child was cortically blind secondarily to Reye's syndrome. One case of blindness due to self-injurious behaviour associated with mental handicap was seen. Finally, one child with Down's syndrome was seen with bilateral phthisis following bilateral retinal detachment.

### CATEGORY NOT ASSIGNED

Seven cases (4%) could not be assigned to the above categories owing to difficulties in arriving at specific diagnoses. Two had tractional detachments of unknown aetiology. One had a pigmentary retinopathy that may have been secondary to a viral retinal pigment epitheliopathy.

### MENTAL HANDICAP

Seventy seven of the 172 cases seen had mental handicap (44·5%). Of those, six had profound handicap, 23 severe, nine moderate, and four mild. The other 35 had not had formal measurement of the intelligence quotient at the time of the survey since they were too young. Most of the latter cases would have been functioning in the 'severe' range as assessed by those caring for them. Seventy five children had developmental delay, usually associated with either mental or physical handicap or both. Twenty six of those with developmental delay, however, were too young to have had a full assessment of their intelligence. Twenty three of this 26 had systemic diagnoses (such as profound cerebral palsy) that made the confirmation of mental handicap at a later date likely. This would then give a total of about 59% with possible mental handicap.

### VISUAL FUNCTION

For the purposes of inclusion in the survey and the register of blind children visual function was assessed in one of several ways by means of the most suitable for the child being examined. In 105 cases this was based on the fixation pattern. Snellen acuity, or perception of light, hand movement, or finger counting were used in 64, and three were assessed by forced choice preferential looking techniques. Visual function was the same in both eyes in 150 children. In 72 cases this consisted of 'uncentral', unsteady, and unmaintained fixation (ucusum) (probably representing a Snellen vision of less than 6/60). A further 28 had central, unsteady, and unmaintained fixation (cusum) (roughly equivalent to a Snellen acuity of 6/60.[3] Twenty three had no perception of light (NPL), 14 had definite light perception (PL), and three had possible PL. Two patients had a Snellen acuity of 1/60 in both eyes and two had 3/60. One child could count fingers and two had hand movement vision bilaterally. Three children had their vision assessed by preferential looking techniques, and their resolving power was estimated at 1·5, 1·3, and 0·32 cycles/degree testing at 38 cm respectively. Visual function was asymmetrical in 22 children. Ten had PL in the better eye, three had HM, three had cusum, two had ucusum, two had 1/60, and two had 3/60, all in the better eye (Table 2).

*Table 2 Visual function by method of assessment*

| | Symmetrical vision | Asymmetrical vision (vision in better eye) |
|---|---|---|
| *Fixation pattern assessment: 105 cases* | | |
| ucusum | 72 | 2 |
| cusum | 28 | 3 |
| *Snellen visual acuity (including NPL, PL, HM, CF): 64 cases* | | |
| NPL | 23+ | 0 |
| PL | 14 (3 ?PL) | 10 |
| HM | 2 | 3 |
| CF | 1 | 0 |
| 1/60 | 2 | 2 |
| 3/60 | 2 | 2 |
| *Forced choice preferential looking. 3 cases* | | |
| 1·5 cycles/degree | 1 | 0 |
| 1·3 cycles/degree | 1 | 0 |
| 0·32 cycle/degree | 1 | 0 |

ucusum=uncentral unsteady unmaintained
cusum=central unsteady unmaintained
NPL=no perception of light
PL=perception of light.
HM=hand movements.
CF=counting fingers.
Where vision was asymmetrical, the vision in the better eye is recorded in this table.

### SURGERY

Eleven patients underwent cataract extraction or clear lens extraction as part of another procedure. Nine had enucleations, seven bilateral, six for retinoblastoma, and one for buphthalmos. Five had had corneal transplantations. Three had vitrectomies and two conventional retinal detachment surgery. Thirty one patients had had surgery of some description (Table 3).

*Table 3 Surgery carried out on children registered (number of procedures)*

| | |
|---|---|
| Cataract extraction/clear lensectomy | 11 |
| Enucleation | 9 (7 bilateral) |
| Corneal transplant | 5 |
| Vitrectomy | 3 |
| Conventional retinal detachment surgery | 2 |
| Squint surgery | 2 |
| Trabeculectomy | 2 |
| Radiotherapy | 2 |
| Probing of nasolacrimal duct | 1 |
| Peripheral iridectomy | 1 |
| Correction of entropion | 1 |
| YAG laser capsulotomy | 1 |
| Removal of band keratopathy | 1 |
| Total patients | 31 |

## Discussion

It has been pointed out in the past that several African and other third world countries have more accurate statistics on the prevalence of blinding disease than the developed nations.[4] Last year the results of the national survey of blindness and low vision in The Gambia were published.[5] A large random stratified sample of this country's population was examined (8174 people). The main causes of blindness found were cataract and uncorrected aphakia, non-trachomatous corneal opacity and phthisis bulbi, and trachoma. Similar studies have been published from Malawi in the past[6] and more recently from Kenya.[7] Two articles in 1989 documented trends in blind registration in two health authorities in the UK.[8,9] Though these latter studies contain accurate and interesting information, it cannot be assumed that they reflect accurately the make-up of the blind population of either the relevant health authorities or the UK as a whole, because the statistics are not derived from a random sample of the population but a highly selected one, namely, those registered as visually impaired in specific areas. Our survey found 108 blind children not previously registered on the Blind Register maintained by the National Association for the Blind in Ireland out of a total of 172 blind children seen (that is, 62·79% were not previously registered). Reliance on registered data is therefore suspect.

For the statistics from any register to be of use the register must actively seek out those visually impaired people in the population, document them accurately (this involves continued review of those registered), and delete those who die or whose acuity improves to a level greater than that at which they would qualify for registration – that is, a 'live' register.

Our study is an attempt to document

accurately the population of blind children (with vision less than or equal to 3/60 in the better eye) in the Republic of Ireland by examining them all ourselves. This information is now incorporated in the Blind Register as the start of a live register. Since such measures of visual function as fixation pattern or even preferential looking do not always correspond with eventual Snellen acuity, some children are registered who will turn out not to be 'blind' by the Snellen criteria set out above. However, this is a live register, and when these children come for review they can be deleted. Because of this we recommend patients should be registered as soon as it is established that their level of visual function, as measured by the most appropriate test available in the individual case, meets the criteria set out. Reliance on Snellen acuity testing as a criterion for blind registration is inappropriate for the preverbal child or for the mentally handicapped.

It is interesting to note that a similar study was carried out in Northern Ireland in the mid 1970s. The ascertainment rate was estimated to be similar to ours, namely 80%.

In Britain several monographs have been published by the Department of Health and Social Security on blindness and partial sight. In recent years these have been confined to the adult population; the most recent containing information on children was published in 1979[10] and referred to the years 1969–76 in England. The information contained in this report is derived from blind registers and not active ascertainment of all cases in the population. The statistics therefore must not be taken as an accurate reflection of the actual incidence and prevalence of the conditions described, but merely as the best available. Our survey, however, has attempted to assess the whole population so that the statistics produced are as accurate as is possible.

The criteria in this study for 'blindness' are stringent by most standards. Legal blindness in the Republic of Ireland is usually taken to be 6/60 or worse in the better eye, or 20° field or worse in the better eye. However, the WHO definition is 3/60 or less in the better eye.[2] For many children a vision of 6/60 does not preclude education by visual methods. Snellen acuity cannot be measured in preverbal infants or in the more severely mentally handicapped. Yet many blind children fall into these categories. For this reason we have set out different, but roughly equivalent, criteria for registration in these groups. An exact correlation between Snellen acuity and fixation pattern or even preferential looking measurements cannot be made, but, as long as those registered are subject to continual review, those patients who with maturation can subsequently be measured by Snellen methods will have this carried out and inappropriate registration altered.

The major causes of blindness in children have been estimated in several publications. The most recent DHSS monograph[10] shows that during 1969–75 in England the commonest causes of new registration in children under 16 were optic atrophy and cataract (no comment is made on the primary systemic diagnoses in these groups, which can vary considerably) followed by congenital abnormalities. In European studies in the mid 1970s in Holland, Belgium, Norway, and Denmark optic atrophy, cataract, congenital abnormalities, and retinopathy of prematurity figured largely also, but many cases of tapetoretinal dystrophy were seen.[11] Foster's review of worldwide statistics concluded that in the developed world childhood blindness was largely due to hereditary causes and factors operating at the time of birth (such as hypoxia).[12] Of note is his comment that better care of preterm infants may have led to an increase in visual handicap.

In countries where there are medical services of intermediate quality intrauterine infections, in particular rubella, are an important preventable cause of blindness. In areas where the medical services are poor, such as many rural and urban slum areas in Asia, Africa, and parts of South America, vitamin A deficiency, measles, and the lack of ophthalmic services are responsible for 50–75% of childhood blindness. Bryars's study in Northern Ireland of visually handicapped children[1] showed that 95% of his cases had pre- or perinatal causes, and 51% were genetic in origin. Of note is the fact that birth injury caused only 2% of his cases. However, 18% were attributed to optic atrophy, with no comment on the primary diagnosis, and presumably some of these are as a result of birth asphyxia. He does note a high incidence of optic atrophy among the mentally handicapped.

In this survey 28 out of 172 (16·28%) had genetically determined disease. This figure is considerably less than those quoted by Baraitser[13] and Jay.[14] Sixty nine cases, however, had causes of their disease that were categorised as prenatal. Many of these had conditions which, though not definitely genetic in origin, may have some genetic background in a multifactorial aetiology, such as optic nerve hypoplasia. It is possible that our strict criteria for inclusion in the genetic category, namely an accurate diagnosis with proved genetic aetiology, may have decreased our total. An associated systemic diagnosis was made in 112 cases (65%). Little reference is made in the DHSS reports (or any of the other large surveys) to this important aspect of the subject. Without this information the significance of a morphological diagnosis such as optic atrophy cannot be assessed, since the aetiology is so diverse.

The commonest morphological diagnoses (which often coexisted in the same patient) were optic atrophy (48 cases), optic nerve hypoplasia (39 cases), and cortical blindness (27 cases). The commonest single causative factor in the first and last of these was birth asphyxia (19 cases). The prominence of optic nerve hypoplasia in this list probably indicates increased recognition of this sometimes subtle condition. A small number have only this isolated abnormality (3 cases) but a great many more are associated with other congenital abnormalities, such as albinism, hydrocephalus, agenesis of the corpus callosum, and septo-optic dysplasia. Retinopathy of prematurity is still a major cause of childhood blindness, seen here in 19 children. However, none of the children so affected were born after September 1987, so perhaps the management of the condition is improving. Recent experience in the field of retinal cryotherapy in this condition gives reason for hope, suggesting a reduction by a half in the numbers of eyes with an unfavourable outcome.[15]

Eleven children were found to be blind owing to tumours. Eight had blinding bilateral retinoblastoma, and three more had intracranial tumours causing damage to the anterior visual pathways (a craniopharyngioma, a hypothalamic astrocytoma, and an optic chiasm glioma).

The two commonest single primary causative agents are prematurity and birth asphyxia, both with 19 cases (11% of the total each). It is important to mention that we did not come across any cases of blindness from bilateral untreated or poorly treated amblyopia. Only three cases of blindness from childhood glaucoma were seen. Rubella eye disease seems to have been almost eradicated, the youngest patient (of only five) was 11 years old. The pattern of diagnoses fits roughly into that seen in other western nations.[12] 44% of the children seen were mentally handicapped. This is similar to other European studies. But if those with developmental delay and diseases likely to lead to mental handicap are included the total is nearer 60%. This can be explained by our confining our study to the severely visually impaired. These children tend to have a higher prevalence of mental handicap.[11]

A large proportion of our cases were under 5 years (46%). This may be attributable to our easy access to the three largest maternity units in the country, all located in Dublin and all referring cases directly to our own paediatric ophthalmology service.

This study shows that almost 30% of the causes of blindness in this country are potentially remediable – genetic causes (16%) through genetic counselling, retinopathy of prematurity (11%), and birth asphyxia (11%) – and 40% cannot be tackled with present knowledge, comprising those prenatal causes that have not yet become amenable to treatment.

One of the chief reasons for undertaking this survey was to upgrade the quality of the ophthalmic and background medical data on the current blind register and to register as many new blind children as possible. The data collected will now constitute the start of a live register to be maintained by the National Council for the Blind in Ireland. A live register would provide information on incidence and prevalence and demographic risk factors, and give invaluable aid to researchers and to those who provide services to the target population.

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# Intraocular coenurosis: a case report

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## Abstract

**A case of intraocular coenurosis was clinically diagnosed and treated with praziquantel. The drug destroyed the coenurus, but vision was lost through toxic endophthalmitis and retinal detachment. There were no systemic side effects.**

Coenurosis is an infection by the cestode larva, the coenurus, which Wardle and McLeod[1] described as a bladder worm with multiple scolices. The particular taeniid species producing the coenuri in man is still controversial, but most accounts of human coenurosis describe the infections as due to the larval forms of *Taenia multiceps*, *T serialis*, or *T brauni*. The adult worms are found in the intestines of carnivorous animals – dog, wolf, fox – while the larvae are usually found in herbivores – sheep, goat, cattle – when these ingest infective eggs expelled from the canines.[2]

Man is a susceptible intermediate host of any of the taeniid species. The oncospheres hatch in the intestine of the intermediate host, penetrate the intestinal wall to reach the blood stream and from there are distributed into various tissues, commonly the central nervous system, the eye, and subcutaneous and intermuscular tissues, where they develop into coenuri.

Most reports on coenurus infections of the eye and adnexa in tropical Africa have come from Uganda, Kenya, and Ghana.[3 4] Two cases have also been reported from South Africa.[5 6] Turner and Leiper[7] first described a human intercostal muscle infection in Northern Nigeria. A case of triceps muscle infection has also been reported from the Northern Nigeria.[2] We here report a new case of clinically diagnosed intravitreal coenurosis in a 25-year-old Nigerian. Details of the clinical course and result of treatment with the schistosomicide, praziquantel, are discussed.

## Case report

A 25-year-old man was referred on 21 September 1987 because of a one-week history of painful redness and blurring of vision in the right eye. His visual acuity was RE 6/9 and LE 6/5 (Snellen's). The right eye showed a tender injection of the temporal sclera with anterior uveitis. He was considered to have scleritis and treated accordingly.

Two months later he reported with further deterioration in vision in the same eye. He also complained of seeing shadows of objects lining up on the surface of a balloon and then sinking back towards its centre. His visual acuity had gone down to counting fingers at 1 metre. A detailed funduscopy revealed a transparent intravitreous cyst located on the temporal side of the retina (corresponding to the area of scleritis) from 7 to 11 o'clock and involving the macula. On the surface of the cyst several white spots were scatted in no definite pattern. There was marked vitreous cellular reaction, but the underlying retina and its vessels were normal. Slit-lamp biomicroscopy showed scolices protruding from the white masses and making pendulum-like excursions in the overlying vitreous. Suckers were clearly visible on most of the scolices. On other occasions the scolices were not visible, having retracted into the white masses. An intravitreous cestode cystic larva with multiple scolices, a coenurus, was suspected.

Investigation into the patient's social history showed that he was a moslem from Plateau State of Nigeria. He never had anything to do with pork or bush meat on religious grounds. He had worked in an agricultural ministry for four years before changing to a mining corporation in Kano State in 1985, and here he had lived in a house with three local dogs.

General examination showed no nodules on any part of the body. The haemoglobin value was 15·5 g/l, leucocyte count $6\times10^9/l$ (neutrophils 45%, lymphocytes 50%, monocytes 2%, and eosinophils 3%). The platelet count was $160\times10^9/l$. Stool examination showed no evidence of parastitic infection. There were no cells in the aqueous humour.

### TREATMENT

The patient was treated with topical steroids, and on 5 February 1988 praziquantel was begun at a daily single dose of 25 mg/kg body weight orally for four days. He also received prednisolone tablets, 10 mg three times daily during the same period.

Ten days later he complained of severe pain and redness in the right eye, noting that the balloon he used to see had become smaller; it then disappeared. Fundoscopy showed that the cyst had ruptured, with the nasal wall floating in the vitreous. Only a few of the white masses were seen lying on the temporal retina, while some white debris lay on the inferior retina. The vitreous was cloudy and visual acuity was hand movements.

Despite a repeat of the course of praziquantel and prednisolone, the patient went on to develop

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endophthalmitis. For this he received three daily doses of periocular dexamethasone injections 4 mg each and was maintained on topical and systemic steroids. When the intraocular inflammation settled, fundoscopy showed a totally detached retina with extensive pre and subretinal fibrosis.

During the remainder of 1988 and throughout 1989 the eye had only occasional flare-ups of intraocular inflammation, which were controlled with steroids. He was last seen on 12 January 1990. Visual acuity was light perception. The eye was comfortable and quiet but the retina remained totally detached, with some white debris scattered on it. The intraocular pressure was normal.

## Discussion

Although only a few cases of intermuscular and no case of coenurosis of the eye have been reported from Nigeria, there is reason to believe that the infection may be commoner than it seems. This is because in this area where animal faecal wastes (dogs inclusive) are deposited indiscriminately in the environment, soil pollution is a big problem, and helminth larvae and ova easily contaminate fresh vegetables and other foods consumed raw.[8] In seven of the 13 cases detailed by Williams and Templeton[3] the infection was intraocular, and the coenurus, as in our case, was in the vitreous. All but one of the patients were adults. Those authors believed that the most likely route of infection in the intraocular and adult cases is the mouth, and is due to eating fresh food contaminated by eggs expelled by the animals (definitive hosts).

As suggested by Kruger-Leite *et al*[9] in the case of intraocular cysticercosis, the larva enters the eye by the posterior ciliary arteries, rests in the subretinal space, and then perforates the retina to reach the vitreous cavity. Most African coenurus infections in children have involved the subconjunctival or subcutaneous tissues. In these cases the larva is inoculated directly into the conjunctiva and skin early in toddler life when these organs are frequently close to contaminated grounds.[3]

When the coenurus is intraocular, the main cause of symptoms appears to be a toxic reaction in contrast to the space-occupying and pressure effects of the coenurus in the central nervous system and in intermuscular and subcutaneous tissues. The development and progress of intraocular inflammation in our case supports this theory of toxic reaction. Toxins released by the cyst induced the iritis and vitritis observed during the initial examination. Following the course of praziquantel, there was disintegration of the cyst and death of the larva. The large dose of toxins so liberated gave rise to the endophthalmitis and loss of vision. The steroids helped contain the intraocular inflammation, though retinal detachment and fibrosis went on to develop.

The best treatment for an intravitreal cestode cystic larva is its removal through a closed vitrectomy.[9] This should be carried out whenever possible and as soon as possible. The cyst should be removed while it is still living,[10] because its death leads to the release of large amounts of toxins and severe intraocular inflammation.

We did not have the facilities for closed vitrectomy, and since scleral dissection would not be the best approach for removal of an intravitreous cyst we decided on medical therapy. We chose praziquantel, a schistosomicide, that has proved effective in destroying cysticerci, including those in the brain and with minimal side effects.[11 12] The drug was easily available at an affordable price. It did prove effective in destroying the coenurus, but the attendant toxic endophthalmitis led to visual loss despite adjuvant systemic steroids. No systemic side effects due to the drug were reported.

Toxic endophthalmitis with its sequelae is the principal mechanism of visual loss when the coenurus is intraocular, but coenurosis can impair vision in other ways. An intracranial coenurus involving the venticular system will lead to symptoms and signs of raised intracranial pressure, including papilloedema. If prolonged, pressure necrosis and visual impairment will ensue. Chiasmal interference or localisation in the cerebral hemispheres will lead to charactersitic visual field defects.

Determination of the particular species to which a coenurus in human infection belongs has been described by Beaver *et al*[2] as difficult, confusing, and at times practically impossible. All the taeniid species that produce coenuri as larvae have the dog as one of the definitive hosts, but they differ in their intermediate host preferences. Our patient had in the recent past worked in agricultural ministry and lived in a house with three local dogs. He was probably infected by taking food or drink contaminated by eggs of worms expelled by the dogs. All the coenurus infections of the eye in tropical and South Africa are said to have conformed to the species *Taenia brauni*.[3 4] In this species the scolices, as in our present case, are distributed haphazardly on the cyst. It is probable that this is another intraocular infection by coenurus of *T brauni*.

Our thanks are due to Mr Shoenekan, RAO (MON) of the Department of Microbiology, University of Jos, for his advice on the parasitology.

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# Treatable blindness in temporal arteritis

J P Diamond

**Abstract**

**Temporal arteritis is a common cause of blindness. Prompt steroid treatment limits unilateral visual loss while protecting the contralateral eye. Established blindness is irreversible. We report a case of temporal arteritis in which an eye with no light perception secondary to an arteritic anterior ischaemic optic neuropathy regained 6/6 vision.**

A 62-year-old Caucasian woman presented to Cheltenham General Hospital in February 1987. She gave a two-month history of generalised malaise, weight loss, pyrexias, proximal myalgia, jaw ache, headache, and scalp tenderness. Corrected visual acuities were 6/5 right and 6/4 left. The erythrocyte sedimentation rate (Westergren) was 110 mm in one hour. A diagnosis of temporal arteritis was made and prednisolone 40 mg started. Seven months later the ESR was 26 mm in one hour, and her prednisolone was decreased to 10 mg daily. Soon afterwards she suffered total loss of vision in the right eye; visual acuity in the left was 6/5. The right eye showed an amaurotic pupil and a swollen optic disc. She also developed a right partial third nerve palsy. The ESR was 40 mm in one hour.

On a daily dose of 60 mg prednisolone her visual acuity in the right eye slowly improved, and three months later it was again 6/6, N 4·5. Colour vision was normal (Ishihara), though Friedmann field analysis showed slight central suppression. The third nerve palsy resolved.

In January 1988 the cycle was repeated, when right vision dropped to 6/60 with recurrent disc swelling. After she had received intravenous methylprednisolone 500 mg daily for two days her right visual acuity again returned to 6/6, N 4·5.

In view of the extraordinary clinical course, temporal artery biopsy was performed 33 months after presentation (Fig 1). The localised loss of the internal elastic lamina and intimal proliferation was consistent was long-standing temporal arteritis.[1]

So far her vision has been preserved on a regimen of combined steroid and azothioprine.

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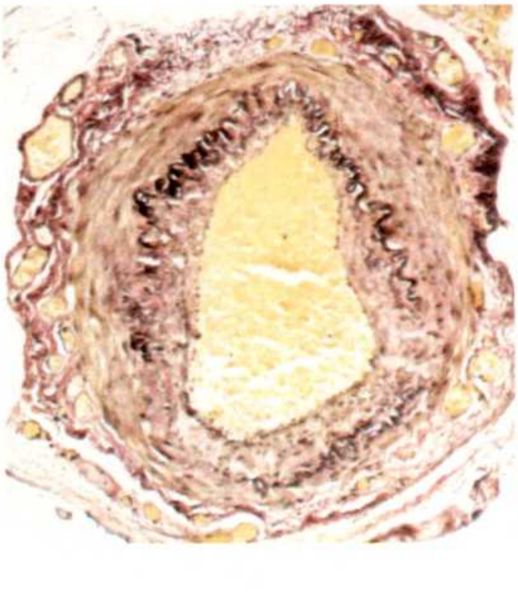

*Figure 1 Photomicrograph of section of temporal artery showing fragmentation of the internal elastic lamina with cellular poliferation within the intima. (×100, elastin stain.)*

## Discussion

Temporal arteritis causes blindness secondary to an ischaemic optic neuropathy, central retinal artery occlusion, or cortical infarction.[2] Although moderate visual recovery is well recognised in arteritic ischaemic optic neuropathy, marked improvement is rare.[2-5] Once established, blindness is irreversible.[6]

Model[3] reported vision improving from light perception to 'normal vision', while Rosenfeld *et al*[7] reported improvements from 20/70 to 20/25. Both patients received methylprednisolone. Schneider *et al*[4] tabulated 22 eyes, five of which improved from no light perception (NLP). None regained 6/6 vision.

Anterior ischaemic optic neuropathy causes an optic nerve conduction defect. Consequent visual loss will be permanent only when axonal infarction supercedes ischaemia. Although this progression usually occurs rapidly, our patient had NLP for several days, suggesting that severe, prolonged ischaemia need not result in permanent axon loss.

Intravenous methylprednisolone is a rare cause of sudden death from cardiac arrythmias.[8] Despite this we recommend considering its use in the treatment of visual loss secondary to arteritic anterior ischaemic optic neuropathy, especially when the second eye is affected.

I thank Mr C T Hart for allowing me to report his patient and Dr B W Codling for the histology.

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# Welding arc maculopathy and fluphenazine

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## Abstract

**A 45-year-old male patient presented with a bilateral maculopathy following unprotected exposure of less than two minutes' duration to a manual metal arc welding unit. He had been receiving the drug fluphenazine for the previous 10 years for treatment of depression. We believe that the drug fluphenazine, which had accumulated in his retinal pigment epithelium, may have rendered him particularly susceptible to retinal photic damage.**

The retina is susceptible to at least three different forms of light damage – thermal, mechanical, and photochemical.[1 2] Thermal damage is produced when the retina is exposed to a temperature rise of 10° to 20°C. Photochemical damage most likely results from longer exposure to bright sources that produce a considerable amount of blue or near ultraviolet light.[3] Light levels required to cause acute photoretinitis are encountered by exposure only to very bright light sources, such as the sun, welding arcs, arc lamps, and tungsten halogen lamp filaments. The type of retinal damage depends on wavelength, energy level, duration of exposure, and degree of pigmentation.[4]

The radiation emitted from welding units covers a wide spectrum, from infrared to ultraviolet and beyond. Excessive exposure to ultraviolet radiation can result in photophthalmia ('welder's flash') and may, under chronic exposure, result in UV cataract.[5 6] Retinal injuries resulting from exposure to welding arc radiation have been reported but are not commonly seen.[7-10] We report here a case of welding arc maculopathy in a patient who had been taking the phenothiazine drug fluphenazine.

## Case report

A 45-year-old man noticed bilaterally decreased visual acuities soon after welding. There was no accurate record of the exact duration of exposure. However, the patient's instructor, who was observing him from a distance, estimated it to be certainly no longer than two minutes. The patient had just begun a training course and had no previous welding experience. He had raised the protective visor which he was wearing in order to see more clearly. This was not noticed by the instructor as the patient was crouched and had his back towards him. He had been using a manual metal arc welding unit with a flux coated rod.

When seen the next day the patient complained of bilateral scotomata and metamorphopsia. At no time did he complain of ocular pain. His best corrected visual acuity was 6/18 in the right eye and 6/12 in the left. The anterior segments were normal. There was no evidence of a punctate keratopathy when the corneas were stained with fluorescein. There was a circular yellow oedematous lesion approximately 250 μm in diameter present at each fovea (Figs 1A, B). Fluorescein angiography carried out five days later was normal. In an effort to demonstrate the capillary-free zone better an enhanced fluorescein angiogram was prepared. The angiogram negative was printed in contact register with an unsharp mask to produce the finished result. This enhanced angiogram demonstrated mild diffuse fluorescence in the foveal avascular zone (Fig 2). The patient was followed up on a regular basis for the next six months. During this period his visual acuities returned to 6/5 in each eye. The results of Amsler grid testing and pattern electroretinograms were also normal in both eyes. Examination of his

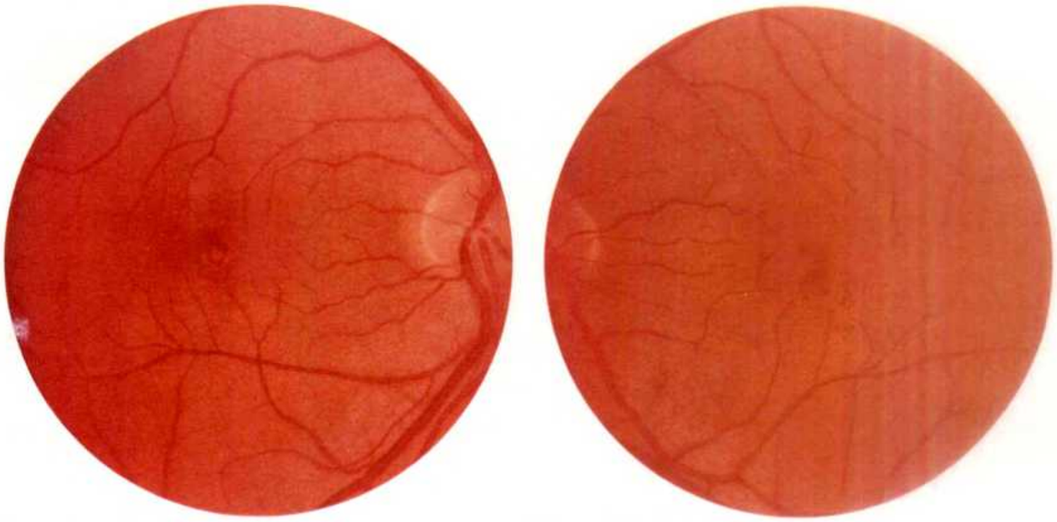

*Figure 1A Right eye.* *Figure 1B Left eye.*

*Figure 1A, B Fundus photographs showing yellow oedematous lesions at both foveas.*

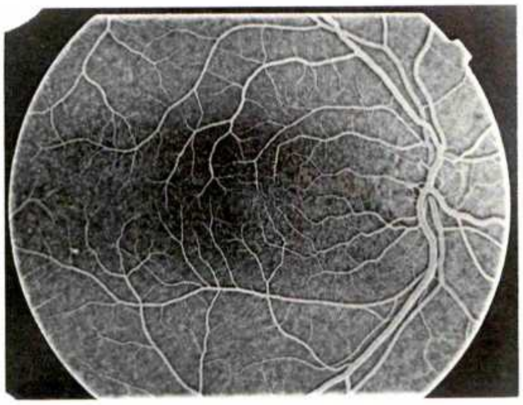

*Figure 2 Enhanced fluorescein angiogram of the right eye, demonstrating fluorescence in the foveal avascular zone.*

fundi at the six-month review showed minimal stippling of the pigment epithelium surrounding each fovea (Figs 3A, B).

The patient was being treated with the drug fluphenazine for endogenous depression. He received 12·5 mg intramuscularly fortnightly for 10 years without interruption. The total estimated dose was calculated to be 3·25 g.

## Discussion

A wide variety of ocular changes are produced by welding arcs, the type of change depending on the wavelength of the arc emissions, the duration of the exposure time, and the power level.[2] The commonest is a keratoconjunctivitis. This is caused by the ultraviolet radiation, which the welding arc produces in large amounts. Welding arc emissions, however, cover quite a wide spectrum, much of which falls within the short or blue wavelengths in the visible spectrum. Photochemical damage to the retinal pigment epithelium and photoreceptors, especially cones, is responsible for retinal damage below photocoagulation threshold. The damage produced is much more pronounced for the short or blue wavelengths in the visible spectrum[11] and is enhanced by increased retinal temperatures.[12 13] Welding arc maculopathy almost certainly represents an example of photochemical injury.

Typically, patients with arc maculopathy complain of a central scotoma and metamorphopsia. Bilateral yellow oedematous lesions at the fovea are characteristic. The lesions measure approximately 200 μm in diameter, even though the size of the arc image is only 20 μm. The 200 μm corresponds to the area about which a fixation point moves because of normal eye movements.[14] The raised lesions, which represent acute retinal oedema, gradually subside over several weeks and are replaced by mottling of the pigment epithelium or occasionally by a small lamellar hole. Most patients recover normal vision, though a few experience a permanent visual deficit.

One of the unusual features of this case is that though the patient was only welding for two minutes he developed a bilateral maculopathy without any evidence of a keratitis. The traditional welding rod, which was used by this patient, produces a relatively greater amount of radiation in the ultraviolet range than the newer metal-arc inert gas welding units.[15] The fact that the patient did not develop a keratitis while exposed to this ultraviolet enriched radiation would seem to confirm the short duration of exposure as reported to us by both the patient and his instructor.

All phenothiazine drugs are deposited in the retinal pigment epithelium to some extent, and most are concentrated there at levels far higher than those found in other body tissues.[16] Quite a number of the phenothiazines, including fluphenazine, have been associated with photosensitising rashes.[17] These drugs may act as psoralens, and it has already been shown that photosensitisation cataractogenesis can be produced in rat lenses when they are incubated with the drug chlorpromazine and irradiated with ultraviolet light.[18]

We postulate that this patient sustained macular burns from welding because the drug which had accumulated in his retinal pigment epithelium over the years may have acted as a photosensitising agent, thereby rendering his retina particularly susceptible to photic damage. The potential role of fluphenazine in this case

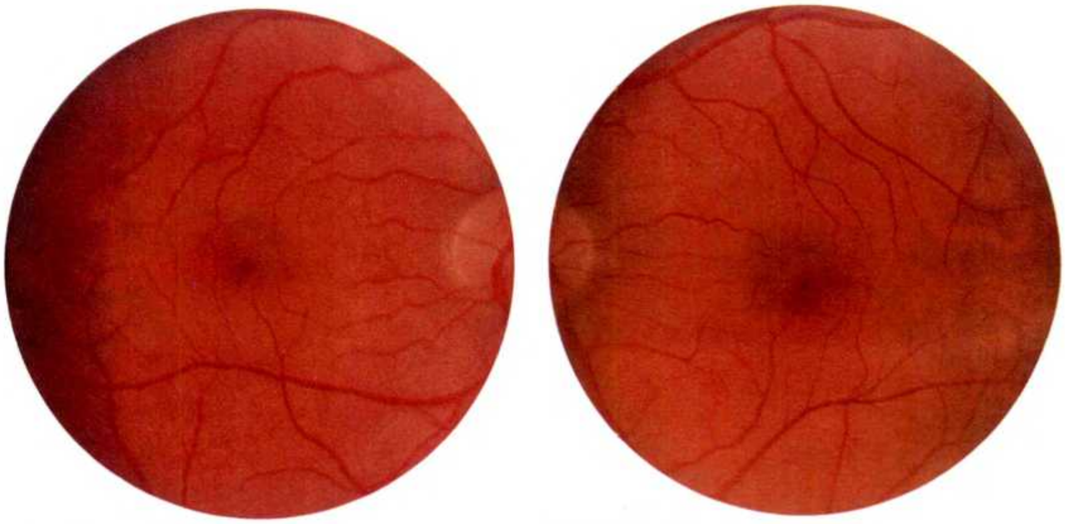

*Figure 3A Right eye.* *Figure 3B Left eye.*

*Figure 3A, B Photographs taken at six months showing pigmentary disturbance at either fovea.*

remains conjectural. However, we believe this is the reason why the patient developed the maculopathy after such a short period of welding.

All patients should take full precautions when welding to avoid inadvertent retinal damage. Patients taking phenothiazine drugs may be at special risk and should be advised accordingly.

We acknowledge Mrs Patricia Conn's secretarial assistance in preparing the manuscript and the help of Mr Kulwant Sehmi, Moorfields Eye Hospital, London, in preparing the subtraction angiogram.

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# Bilateral retinal artery occlusion due to mitral valve prolapse

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## Abstract

**We report a case of bilateral retinal artery occlusion due to mitral valve prolapse. Most patients with retinal ischaemia in whom it is found have not been previously known to have it. Since it is a common condition it would seem essential that it be included in the differential diagnosis of amaurosis fugax and retinal artery occlusion if future ischaemic events are to be prevented. All patients with retinal ischaemia should have a full cardiovascular examination supplemented by echocardiography.**

Several cardiovascular causes of retinal ischaemia have been described including rheumatic valvular heart disease, calcified aortic disease, subacute bacterial endocarditis, valvular prostheses, cardiac myxomata, and carotid artery atherosclerosis. Mitral valve prolapse (MVP) is the commonest form of valvular heart disease in adults, and it has been increasingly recognised that it is associated with thromboembolism, including embolic phenomena in the ophthalmic circulation. MVP is easily missed, since these patients may have few cardiac symptoms or physical signs. Patients with it may first present with amaurosis fugax or rarely retinal artery occlusion, and awareness of the disease is therefore important to the ophthalmologist. We describe here a patient with bilateral retinal artery occlusion due to idiopathic prolapse of the mitral valve.

## Case report

A 69-year-old woman presented with sudden painless loss of vision of the right eye followed six hours later by diminished vision in the inferonasal field of the left eye. There was no previous history of transient ischaemic attacks, amaurosis fugax, or rheumatic fever. She denied having had chest pain, dyspnoea, or palpitations. Essential thrombocythaemia had been diagnosed 10 years previously and was successfully treated with a single dose of radioactive phosphorus. Her platelet count had remained normal since.

Ocular examination showed a dense relative right afferent pupil defect with no light perception in the right eye and 6/9 vision in the left. Funduscopy revealed occlusion of the central retinal artery in the right eye due to a white refractile embolus lodged at the disc centre. Severe retinal oedema with a cherry red spot in the macula and supramacular haemorrhages were noted, while the peripheral retina had a normal non-ischaemic appearance (Fig 1). The embolus at the disc did not glisten with arterial pulsation or change position. In the left fundus an embolus was present in one of the superior arteriolar branches, leading to retinal oedema confined to the superotemporal quadrant. Field examination to confrontation of the left eye confirmed an inferior field defect, and on the Amsler grid the patient could point out a dense inferior scotoma.

Physical examination revealed no evidence of hypertension, subacute bacterial endocarditis, or carotid artery bruits. However, a midsystolic click followed by a late systolic murmur was heard at the apex. Echocardiography confirmed the presence of thickened mitral valve leaflets, both of which prolapsed during systole (Fig 2). The left atrium was dilated, but no thrombus was found (Fig 3). A 12-lead electrocardiogram was normal, but 24-hour electrocardiographic monitoring detected brief (less than 9 seconds) asymptomatic episodes of atrial fibrillation (150 beats per minute). Ultrasonography and Doppler studies of the neck revealed no significant atheromatous disease of the carotid arteries. Laboratory investigations showed Hb 14·5 g/dl, leucocytes $9{\cdot}5\times10^9$/l, and platelets $400\times10^9$/l. The erythrocyte sedimentation rate was 9 mm in the first hour. Further laboratory studies including urea and electrolytes, liver function tests, blood glucose, autoantibody screen, serum protein electrophoresis, platelet function tests, triglycerides, and cholesterol gave results within normal limits.

Treatment was instituted with warfarin and aspirin. Her visual acuity has not improved, but she has so far had no further episodes of cerebral or retinal ischaemia.

## Discussion

The incidence of MVP in the general population is 2·5% to 5%.[1] Although it was initially thought to be a benign disorder, it has now been associated with subacute bacterial endocarditis, mitral

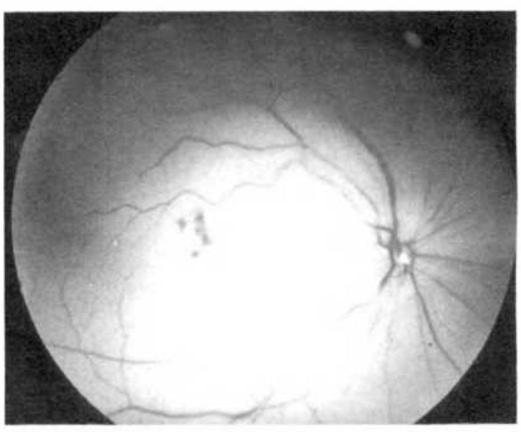

*Figure 1: Refractile embolus lodged in right central retinal artery. Cherry red spot and supramacular haemorrhages noted.*

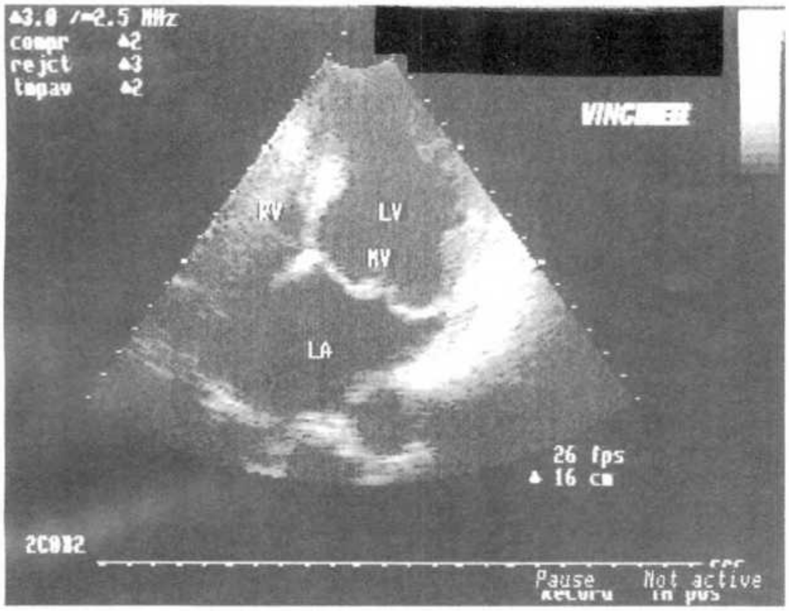

*Figure 2: 2D – Echocardiogram. Prolapse of both mitral valve cusps into the left atrium during systole. LA=left atrium. LV=left ventricle. RV=right ventricle. MV=mitral valve.*

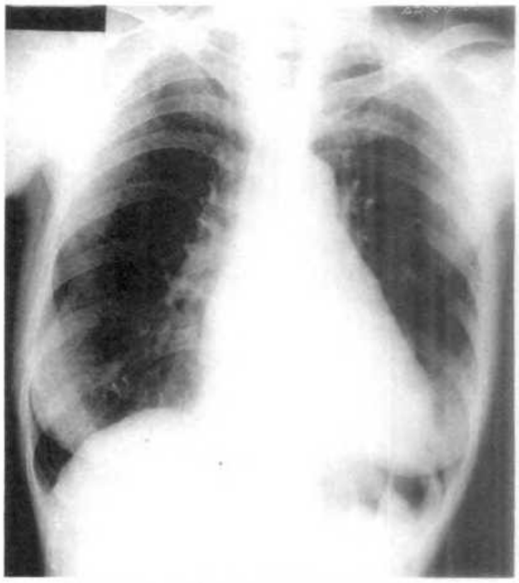

*Figure 3: Chest x ray showing bulging of the left heart border due to enlargement of the left atrium.*

regurgitation, atrial and ventricular dysrhythmias, and sudden death. Reported thromboembolic complications include transient ischaemic attacks, stroke, amaurosis fugax, and rarely retinal artery occlusion.[2] Symptoms of MVP are atypical chest pain, palpitations, syncope, and dyspnoea. On auscultation a characteristic mid systolic click followed by a late systolic murmur may be heard, while sitting, standing, and the Valsalva manoeuvre all accentuate the murmur.[3] Two-dimensional echocardiography confirms the diagnosis.

Our patient is unusual in having simultaneous bilateral retinal artery occlusion, which strongly suggests a cardiac origin of the emboli. Retinal examination revealed the typical calcific emboli associated with valvular heart disease and sudden permanent loss of vision.[4] Visual and neurological dysfunction in essential thrombocythaemia is associated with the presence of thrombocytosis and spontaneous platelet aggregation. Since both platelet count and platelet function were normal, it is unlikely that essential thrombocythaemia should be implicated as the cause of her emboli.[5] Ultrasonography and Doppler flow studies of both carotid arteries gave no evidence of atheromatous plaques as a source of emboli.

Most patients with cerebral or retinal ischaemic attacks in whom MVP is found have not been previously known to have MVP.[6] The cardiovascular examination may be entirely normal and the history negative.[7] These patients may first present to the ophthalmologist, and it is important that MVP should be included in the differential diagnosis of amaurosis fugax and retinal artery occlusion if further thromboembolic episodes are to be prevented. All patients presenting with retinal ischaemia should have a thorough cardiovascular assessment followed by echocardiography.

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# Solitary extramedullary plasmacytoma of the maxillary antrum and orbit presenting as acute bacterial orbital cellulitis

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## Abstract

**Orbital involvement by plasma cell tumours is rare. Orbital tumours do not generally present as an acute orbital inflammatory disease in adults, though tumours such as rhabdomyosarcoma may cause clinical signs similar to an acute orbital cellulitis in children. We describe a patient with bacterial orbital cellulitis and sinusitis who was found to have an extramedullary plasmacytoma of the maxillary antrum and orbit and coexisting testicular seminoma.**

A 56-year-old previously healthy male, presented with a one-week history of right-sided orbital pain, blurred vision, and vertical diplopia. Visual acuity (Snellen) was 6/9 in the right eye and 6/6 in the left. The right eye showed 2 mm of ptosis, 3 mm of proptosis, and 3 mm of downward displacement of the globe. There was a fluctuant mass at the outer canthus with associated periorbital oedema and some conjunctival chemosis (Fig 1). There was a right relative afferent pupil defect and restriction of right up gaze. Funduscopy showed normal appearances. The left eye was normal. The right nostril was discharging pus, and right infraorbital nerve anaesthesia was present. The sublingual temperature was 38°C.

Plain *x* rays showed opacity of the right antrum. Bacterial orbital cellulitis secondary to sinusitis was suspected. Intravenous antibiotics were prescribed, following which there was gradual improvement in symptoms and orbital signs. A maxillary antral washout was carried out and swabs from the right antrum grew *Steptococcus pneumoniae*. A computed tomogram of the maxilla and orbit revealed an extensive mass filling the right maxillary antrum, eroding the medial and lateral walls of the antrum and orbital floor, with tumour extending upwards into the orbit and encompassing the inferior aspect of the optic nerve (Fig 2). At the most posterior aspect the pterygoid plates were involved, but the mass did not extend through the base of the skull. Antral biopsies revealed large numbers of plasmacytoid cells, plasma cells, and less differentiated forms with large nucleoli. Mitoses, pleomorphism, and apoptotic cells were all present (Fig 3). Extramedullary plasmacytoma was diagnosed.

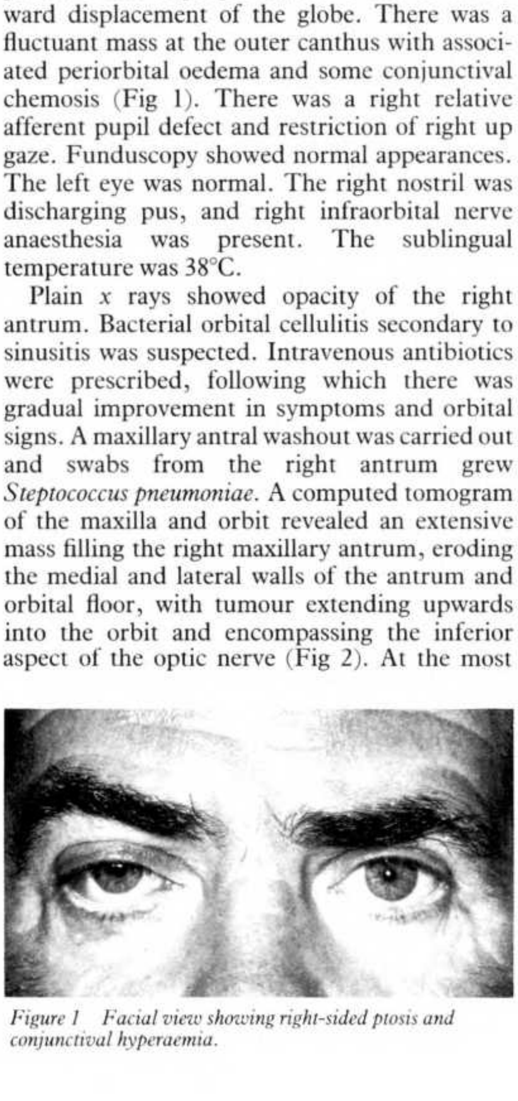

*Figure 1 Facial view showing right-sided ptosis and conjunctival hyperaemia.*

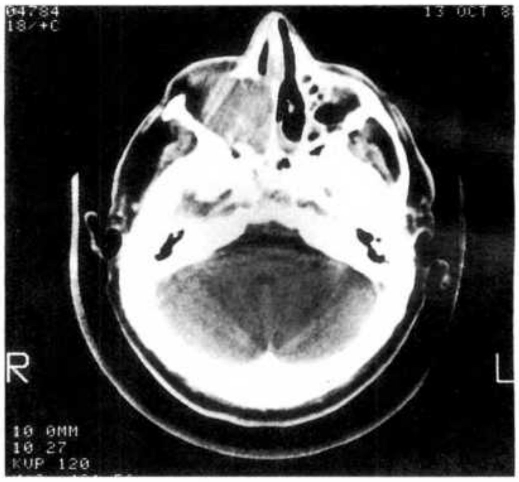

*Figure 2 CT scan: coronal section through maxillary sinuses revealing an opaque right antrum with extensive destruction of its medial and lateral walls.*

Oncology consultation revealed an asymptomatic testicular mass. Further investigations showed no evidence of multiple myeloma on skeletal *x* rays, and normal findings for serum immunoglobulins, electrophoresis, light chain urinary excretion, bone marrow aspiration, and trephine biopsy. A right orchidectomy was subsequently performed. Histologically it was an anaplastic seminoma. Radiotherapy to the right maxillary antrum, orbit, and para-aortic areas was given. The patient remains well at 18 months follow up.

## Discussion

Multiple myeloma is a disseminated plasma cell dyscrasia characterised by marrow infiltration, multiple erosive bony lesions, and the production of a monoclonal protein. Ocular manifestations of multiple myeloma such as corneal and conjunctival deposition of crystals, and retinal and proteinaceous pars plana cysts, are due to the hypergammaglobulinaemia and/or changes in blood rheology.[1,2] Infiltration of the uveal tract can also occur.[1,3]

Solitary plasma cell tumours of bone or of soft tissues (extramedullary plasmacytoma) can occur independently of multiple myeloma.[4] Extra-

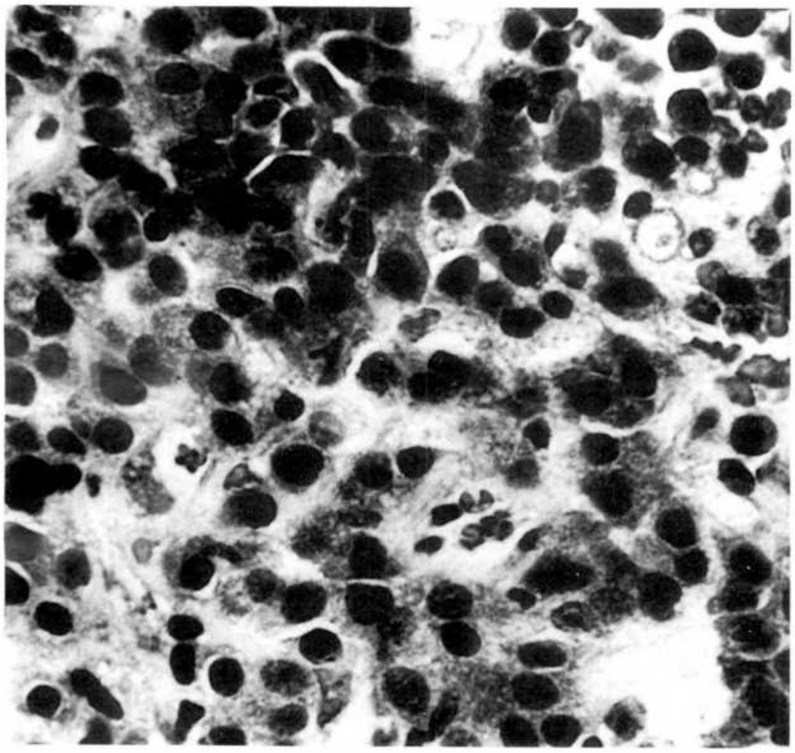

*Figure 3 Histology of antral plasmacytoma showing pleomorphic plasma cells and plasmacytoid cells, some containing large nucleoli. (H and E, ×250.)*

medullary plasmacytomas represent only 3% of plasma cell neoplasms and occur mostly in the upper respiratory tract. Those affected have a mean survival of 192 months compared with a mean survival of 30 months for multiple myeloma.[4]

Extramedullary plasmacytomas of the orbit have been described in 10 patients.[5,6] Prolonged follow-up or complex investigations are required to establish that the orbital disease is not an early manifestation of multiple myeloma. Over 30 cases have been recorded of multiple myeloma involving the orbit, most of which had evidence of disseminated disease on presentation.[1,5,6] Orbital involvement usually presents with slowly progressive proptosis. Our patient, in marked contrast, presented with acute bacterial orbital cellulitis. De-Smet and Rootman described a patient with known systemic multiple myeloma who presented with a possible orbital cellulitis.[6] Frontal sinus biopsy confirmed malignant plasma cells, and despite chemotherapy death occurred from intracranial extension. Mustoe *et al* described a patient with a febrile sinus infection, unresponsive to seven weeks of intravenous antibiotics, in whom an eventual histological diagnosis of plasmacytoma was made.[7] That patient responded well to radiotherapy, the treatment of choice for solitary plasmacytomas.[8]

Our case emphasises the importance of a computerised tomogram of paranasal sinuses and orbits and of obtaining tissue for histological study – for example by paranasal sinus trephination – in the management of such patients.

A second rare type of neoplasm, a testicular seminoma, was also discovered in this patient. Histologically the two tumours were completely distinct. Simultaneous presentation of multiple tumours is recognised, though unusual. An enhanced susceptibility to mitotic lesions has been postulated. A specific oncogene may be responsible.

The ophthalmologist managing a patient with an orbital neoplasm requires the combined skills of a multidisciplinary team. Oncology, radiotherapy, otolaryngology, neurosurgery, neuroradiology, and orbital pathology services may all be required.

We are grateful to Dr R E Bonshek, Department of Ophthalmic Pathology, and to Dr D Martin, Department of Diagnostic Radiology, at the University of Manchester for their expert help. The patient was under the care of Mr K B Mills, FRCS.

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# Late onset endophthalmitis associated with intraocular lens: a case of molecularly proved *S. epidermidis* aetiology

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## Abstract

**A case of severe endophthalmitis after cataract extraction followed by posterior chamber lens implantation is reported. Microbiological cultures from a tap of the patient's aqueous humour prior to lens explantation as well as from the explanted lens and aqueous and vitreous humour during operation yielded *Staphylococcus epidermidis* sensu stricto. Scanning electron microscopy showed massive colonisation of the lens loop by staphylococci. Clonal identity of all isolates was demonstrated by plasmid DNA analysis and sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) of extracellular products. This is strongly suggestive of the aetiological role of *S. epidermidis* in this case of late onset endophthalmitis.**

Coagulase-negative staphylococci – in particular *S. epidermidis* sensu stricto – are the commonest organisms isolated from foreign body infections.[1] The pathogenesis of these infections is characterised by the ability of these bacteria to adhere to and grow on polymer surfaces and to produce an extracellular slime substance which protects the embedded bacterial cells against the host's immune response and antibiotic therapy.[2,3] Moreover, *S. epidermidis* is regarded as one of the commonest micro-organisms isolated in late onset endophthalmitis.[4] However, until now its aetiological role in these infections has not been proved, mainly because of the lack of an adequate animal model.

Here we report a clinical case in which a patient developed a recurrent endophthalmitis after intraocular lens implantation. The *S. epidermidis* strains isolated from the anterior chamber before surgery and isolates from the infected lens, aqueous humour, and anterior chamber after surgery showed clonal identity as determined by molecular methods.

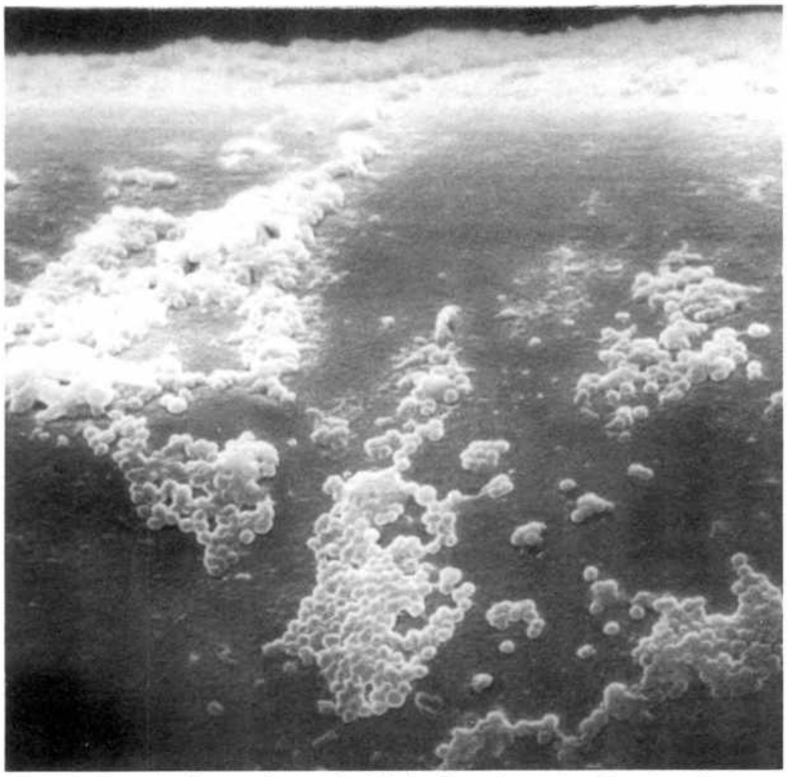

*Figure 1 Scanning electron micrographs of the lens loop after explantation. A massive colonisation by staphylococcal cells can be seen.*

## Case report

An 81-year-old man underwent an extracapsular cataract extraction followed by posterior chamber lens implantation in July 1987 in another hospital. On the third day after operation inflammation of the eye with fibrin deposition and hypopyon were diagnosed. The posterior segment was also affected, showing massive vitreous infiltrates; in addition there was a transient corneal oedema. On treatment with steroids and antibiotics (substances and doses not known) all inflammatory signs slowly regressed. Nevertheless, there was continuous inflammation of the entire eye.

In January 1988 the patient was seen in our clinic with severe endophthalmitis and treated again with antibiotics (cefotaxime 2 g three times a day, gentamicin 40 mg/40 mg/60 mg intramuscularly per day), high doses of steroids (prednisolone 150 mg per day), and topical subconjunctival injections of steroids and antibiotics. Paracentesis of the anterior chamber was performed and the aqueous humour submitted for culture and microscopical examination, as inflammation with hypopyon and vitreous infiltration persisted. Two weeks later the intraocular lens was explanted together with the capsular bag, and vitrectomy was performed. The lens, aqueous humour, and vitreous humour were examined by microbiological methods. In the three months following the second operation the inflammation slowly regressed. The final visual acuity was 0·5 in comparison with light perception and intact light projection before surgery.

Microbiological cultures from a tap of the patient's aqueous humour prior to lens explantation as well as from the explanted lens and aqueous and vitreous humour during the operation all yielded coagulase-negative staphylococci.

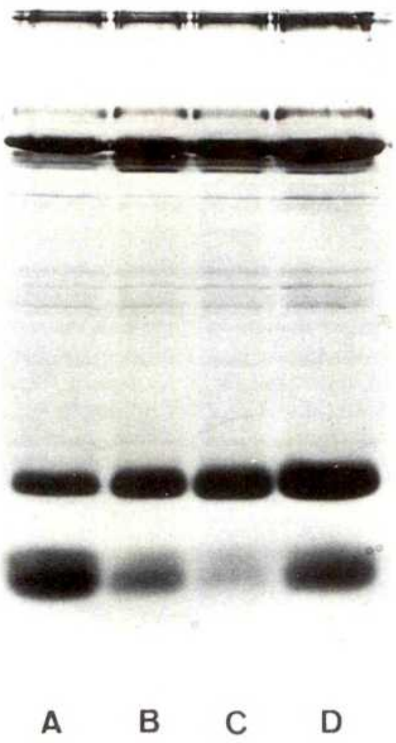

*Figure 2A Sodium dodecylsulphate-polyacrylamide gel electrophoresis (SDS-PAGE) of crude extracellular products of the four isolates of* S. epidermidis.

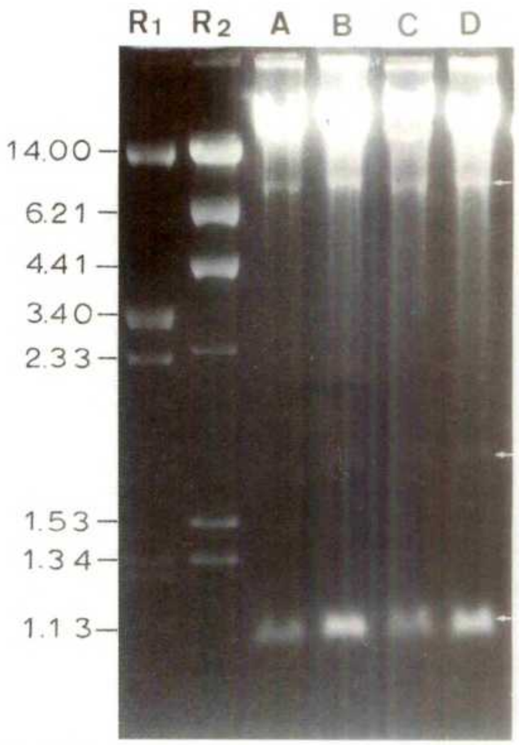

*Figure 2B Agarose gel electrophoresis of plasmid DNA of the four isolates of* S. epidermidis *(molecular mass markers in megadaltons).*

Scanning electron micrography of the lens loop (Prolene) showed massive colonisation by staphylococcal cells (Fig 1). Identification by the method of Kloos and Schleifer[5] showed in all four cases *S. epidermidis* sensu stricto. The antimicrobial resistance pattern was also identical for the four isolates, showing resistance of the strains to penicillin, ampicillin, cotrimoxazole, and tetracycline. To demonstrate identity at the molecular level sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE, Fig 2A), and analysis of plasmid profiles (Fig 2B) were performed, showing identical patterns for the four isolates with both methods.

## Discussion

There are a number of reports of intraocular infections presumably caused by *S. epidermidis* after intraocular lens implantation following cataract surgery.[6] In addition, the ability of *S. epidermidis* to adhere to and to colonise synthetic polymers has been demonstrated.[7,8] Recently, it was also shown that *S. epidermidis* can adhere to intraocular lenses.[9] However, it has not yet been proved that it can cause this type of infection, mainly because of the lack of an adequate animal model. Furthermore, coagulase-negative staphylococci are normal colonisers of skin and mucous membranes and often found as contaminants in clinical material. The clonal identity of coagulase-negative staphylococcal strains obtained from different sites (such as infected lens, aqueous humour, anterior chamber) and at repeated intervals has not been demonstrated in any of the studies published so far.

In the case presented here we isolated *S. epidermidis* from the explanted lens and demonstrated by scanning electron microscopy that staphylococcal cells were adherent to the lens loop embedded in a matrix of extracellular slime (Fig 1). All the *S. epidermidis* isolates cultivated from the lens, aqueous, and vitreous humour showed identity on the molecular level as shown by plasmid DNA analysis and SDS-PAGE. To our knowledge this is the first report in which the clonal identity of *S. epidermidis* obtained from different sites and at repeated intervals could be demonstrated in a patient with intraocular infection after lens implantation. The findings are strongly suggestive of the aetiological role of *S. epidermidis* in this case of intraocular lens-associated late onset endophthalmitis. Thus this entity may be characterised as a chronic polymer-associated *S. epidermidis* infection.

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# Ptosis caused by pachydermoperiostosis

J N P Kirkpatrick, P H McKee, D J Spalton

**Abstract**

**Pachydermoperiostosis is a rare inherited disorder which presents with finger clubbing, facial enlargement, and periostitis. A case is described in which surgery for ptosis was performed and the differential diagnosis of the condition is discussed. The histological and ultrastructural appearances of the eyelids show sebaceous gland hyperplasia and excessive deposition of mucin in the dermis and would suggest that pachydermoperiostosis may be an example of a cutaneous mucinosis.**

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Pachydermoperiostosis (Touraine-Solente-Gole syndrome) is a rare inherited syndrome of unknown aetiology in which hypertrophic changes in skin and bone simulate acromegaly. The condition was first described in two brothers by Friedrich in 1868, when it was considered to be an example of acromegaly.[1] In 1935 Touraine, Solente, and Gole postulated that pachydermoperiostosis was a separate conditon quite distinct from acromegaly or the syndrome of hypertrophic pulmonary osteoarthropathy.[2]

The mode of inheritance of the disease is unclear, but an autosomal dominant pattern with varying expressivity has been suggested.[3] It is commoner in males, with only a few reported female cases, in whom features of the disease are less marked. The condition presents at puberty, with progression of features into early adult life, after which there is little change. Soft tissue hyperplasia in hands and feet with marked clubbing at the digits occurs. The skin of the face and forehead is thickened and folded, and sebaceous hyperplasia is present. In addition, there may be extensive sagittal folding of the scalp, a condition known as cutis verticis gyrata. Bones show a periostitis and periosteal new bone formation, with resultant increase in circumference without a reduction in bony strength. Patients may complain of sweating due to hyperhidrosis of hands and feet, but pain is not a feature of this condition in contrast to hypertrophic pulmonary osteoarthropathy.

We report on a patient with this condition who presented with ptosis, and the histopathological features in the eye lids are discussed.

## Case report

A 24-year-old male complained of difficulty in opening both eyes and the presence of crusts on the eyelid margins, particularly in the mornings. Pachydermoperiostosis had been diagnosed at puberty. His brother was also affected.

On examination the typical features of gross clubbing, 'watchglass' fingernails, and enlargement of the hands (Fig 1) and feet were noted. There was marked thickening of the skin of the face and forehead, which appeared furrowed and oily (Fig 2). There were no signs of prognathism or macroglossia. Visual acuity was correctable 6/5 in both eyes; colour vision, pupillary responses, ocular movements, and intraocular examination were normal. Examination of the eyelids showed that the palpebral apertures were reduced to 5 mm bilaterally, with an S-shaped curve of the upper lid margins (Fig 3A). With the lids closed there was so much redundancy that the upper lids tended to override the lower lids. The skin of the eyelids was thickened, and the tarsal conjunctiva showed a marked papillary response (Fig 3B). The tarsal plates appeared lax, with a vertical height of 14 mm bilaterally. There was good levator function.

Initially surgery was performed on the right upper lid. A 4 mm tarsectomy of the tarsal plate was performed via a conjunctival approach, and the lid was shortened by wedge excision. A similar procedure was performed on the left upper lid a few weeks later. The patient made an uncomplicated recovery and had an excellent cosmetic result. Tissue from both eye lids was submitted for histological examination and electron microscopy.

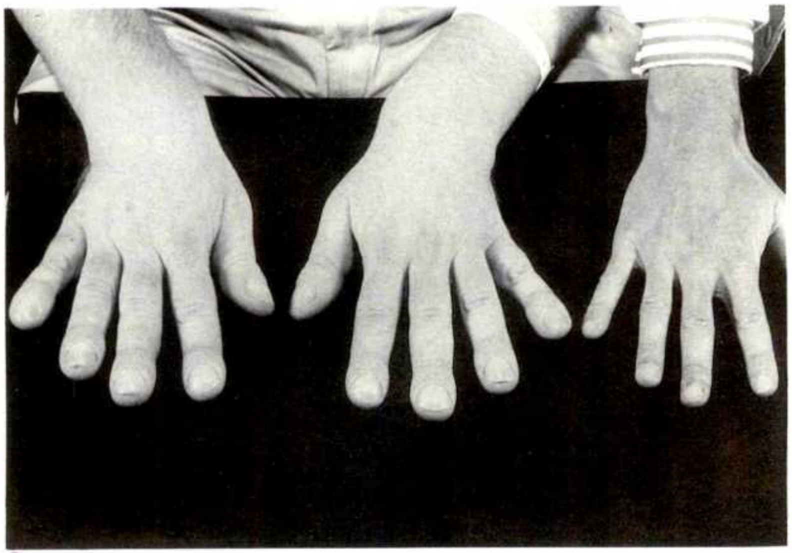

*Figure 1 Clubbing and enlargement of hands in pachydermoperiostosis compared with a normal adult hand.*

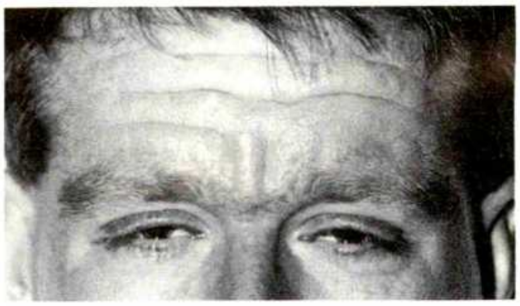

*Figure 2 Furrowing of forehead and bilateral ptosis.*

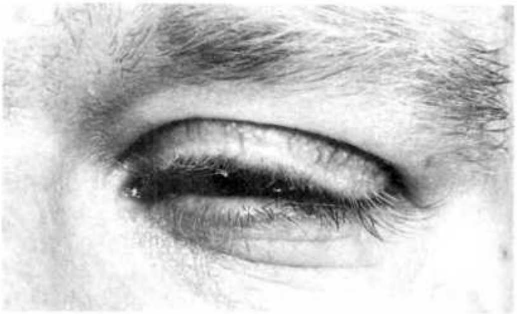

*Figure 3A Ptosis and lid thickening of the left eye: note the S-shaped curve of the upper lid margin.*

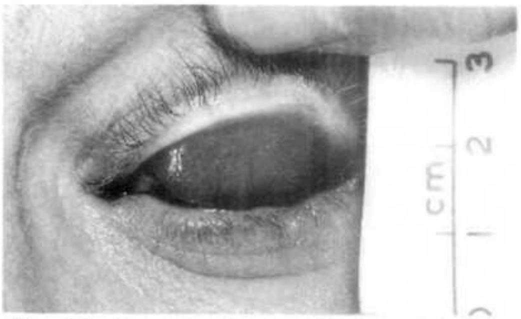

*Figure 3B On eversion there is papillary hyperplasia of the tarsal conjunctiva. The vertical dimension measures 14 mm.*

## Materials and methods

The specimens were fixed in 10% formaldehyde and paraffin embedded. Sections 4 μm thick were stained with haematoxylin and eosin, periodic acid Schiff with and without diastase predigestion, alcian blue at pH 0·5, 1·0, and 2·5 with and without hyaluronidase pretreatment, elastic van Gieson, Masson's trichrome, toluidine blue, and chloracetate esterase.

Fresh tissue was diced into approximately 1·0 mm cubes and fixed in 2% glutaraldehyde. They were post-fixed in 1% osmium tetroxide, dehydrated, and embedded in Araldite. Following examination of a 1·0 μm, toluidine blue stained 'semi-thin', section, sections from selected regions were cut 80 nm thick with an LKB ultramicrotome and stained with lead citrate and uranyl acetate. They were examined in a Philips 201 electron microscope at 60 kV.

## Results

Both eyelids showed similar features. Most conspicuous was the presence of sebaceous gland hyperplasia. Focal accumulations of mucin, situated predominantly around blood vessels and adnexae, were also present in the dermis (Fig 4). In places they were associated with stellate fibroblasts (Fig 5). The mucin was focally periodic acid Schiff positive and stained with alcian blue at pH 2·5. This was completely abolished by pretreatment with testicular hyaluronidase, confirming that the mucin was composed of hyaluronic acid. Patchy fibrous scarring was present in addition to a heavy chronic inflammatory cell infiltrate consisting of lymphocytes and plasma cells adjacent to the palpebral conjunctiva. Very large numbers of mast cells were widely distributed throughout the eyelids (Fig 6). The tarsal plate histology appeared normal.

Ultrastructurally the sebaceous glands and apocrine glands appeared normal. No morphological abnormality of the fibrous connective tissue components was seen. The only consistent lesion was marked reduplication of the basal lamina surrounding the dermal blood vessels (Fig 7).

## Discussion

Perhaps the most important differential diagnosis

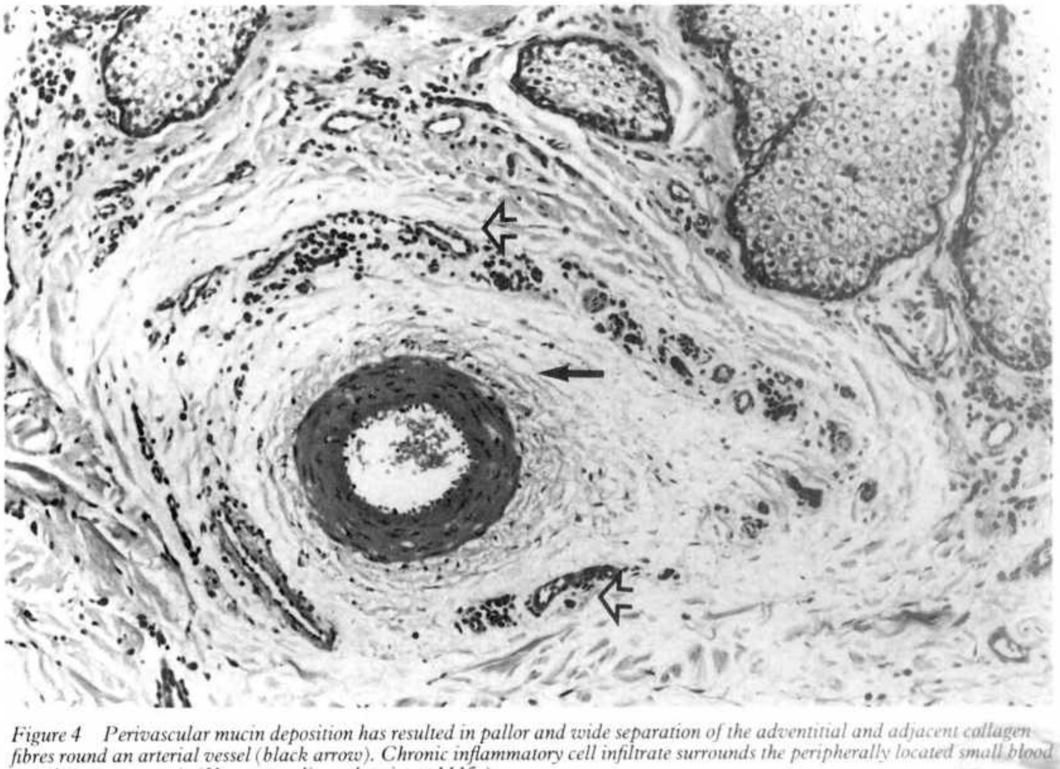

*Figure 4 Perivascular mucin deposition has resulted in pallor and wide separation of the adventitial and adjacent collagen fibres round an arterial vessel (black arrow). Chronic inflammatory cell infiltrate surrounds the peripherally located small blood vessels (open arrows). (Haematoxylin and eosin, ×1115.)*

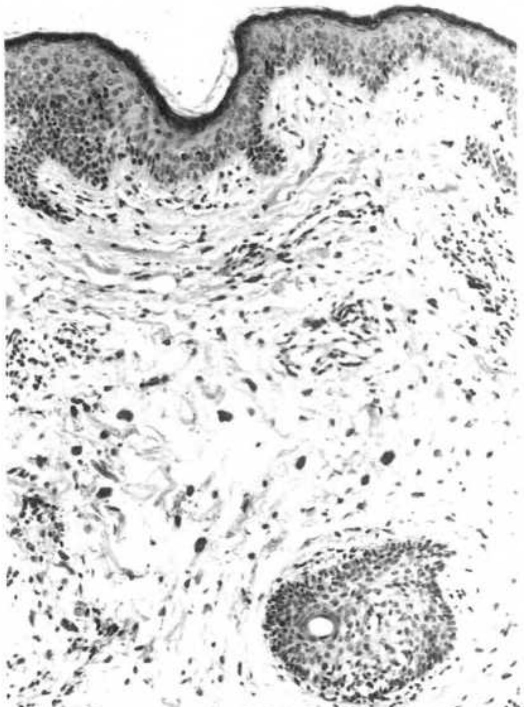

*Figure 5 Mucin deposition in the mid dermis associated with hyperchromatic atypical fibroblasts. (Haematoxylin and eosin, ×80.)*

of pachydermoperiostosis is acromegaly, which is differentiated by the typical bony changes as well as increase of serum growth hormone levels. A number of other rare conditions can produce similar appearances. Pachydermoperiostosis may be clinically identical to hypertrophic pulmonary osteoarthropathy, but distinguishing features of the former include the lack of pain and the absence of an underlying bronchial lesion (usually carcinoma).[4] Abnormal facies such as the leonine facies of leprosy, congenital syphilis, and myxoedema may enter the differential diagnosis. Radiological features of affected digits should be differentiated from rheumatoid arthritis, Paget's disease, and periostitis. Unusual eyelid thickening and facial abnormalities have been described in Ascher's syndrome (acquired double lip, blepharochalasis, and non-toxic goitre[5]), in neurofibromatosis, and in the syndrome of multiple endocrine neoplasia type II B, in which lid thickening is caused by neuroma formation in the dermis and conjunctiva of the eyelids.[6]

Ocular features in pachydermoperiostosis are mainly related to ptosis and chronic tarsitis. Ptosis is often not severe, and there are few reported cases in which surgery has been required. Davidson and Smith[7] described excision of an ellipse of the upper lid with some success, and more recently Ohtsuka and Takayangi[8] described a three-stage procedure of lid shortening, upper lid tarsectomy, and blepharoplasty. In our case lid shortening and tarsectomy were performed at one sitting with no evidence of delayed or abnormal healing, as was postulated by Ohtsuka and Takayanigi.[8] Other reported ocular associations with pachydermoperiostosis include corneal leucoma,[7] cataract formation,[9] and presenile macular dystrophy.[10]

The findings on light microscopy of the eyelids in this case are in accordance with those described previously,[7 11] and the cutaneous features are similar to those found elsewhere in the skin. These include sebaceous gland hyperplasia, enlargement of sweat glands, thickening of the dermis with an increase in collagen content, deposition of mucin, and perivascular lymphocytic infiltration.[12 13] In our case sebaceous hyperplasia and dermal mucin deposition were the most prominent of those features and contributed to eyelid thickening and thus the development of ptosis. This contrasts with the

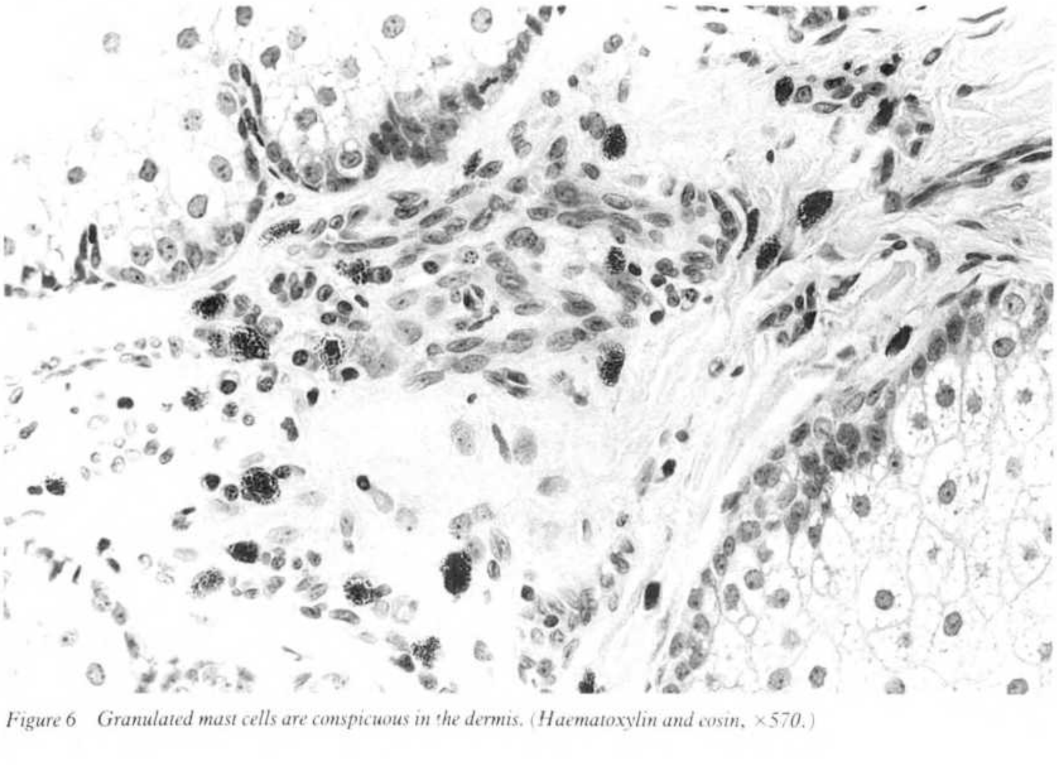

*Figure 6 Granulated mast cells are conspicuous in the dermis. (Haematoxylin and eosin, ×570.)*

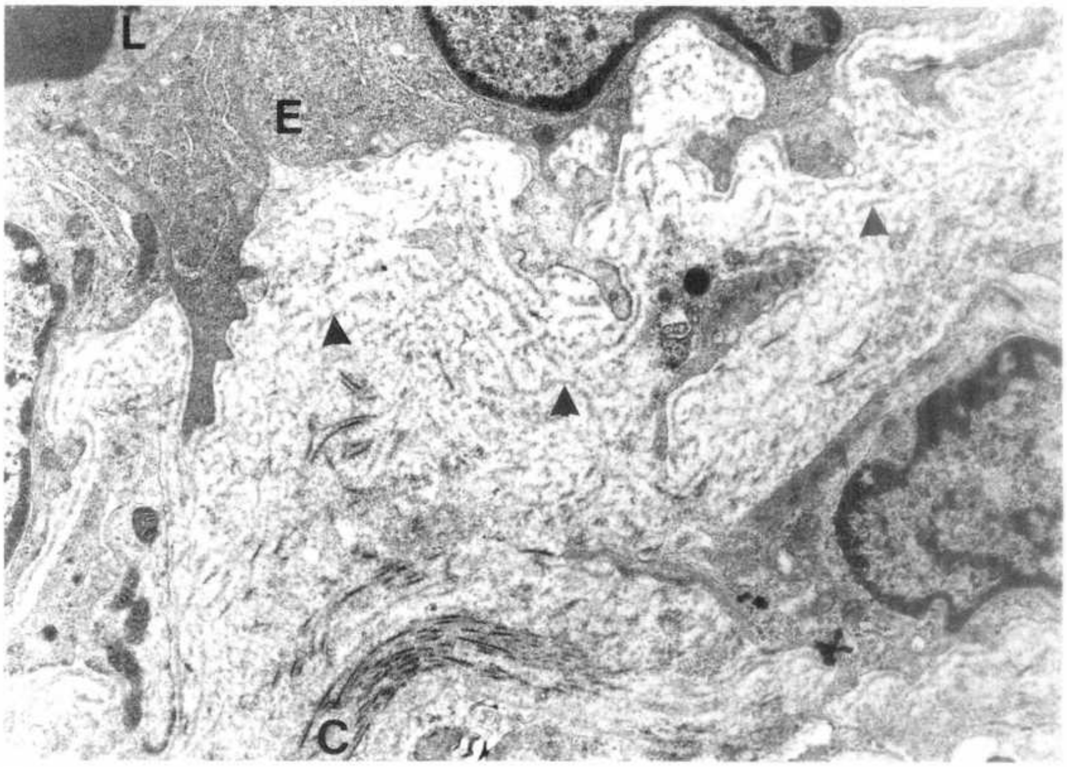

*Figure 7 Electronmicrograph showing extensive reduplication of the basal lamina (arrowheads) of a dermal venule. (× 12 320.) L = lumen. E = endothelial cell. C = collagen.*

marked tarsal plate scarring reported by Downes *et al*,[11] who postulated that the basic abnormality was a hyperplasia of the sebaceous and meibomian glands with secondary inflammatory changes of the tarsal plate. The conjunctival appearance of macroscopic papillary response and a microscopic chronic inflammatory infiltrate with increase in goblet cell numbers has been described[5 6]; it may be a non-specific feature of reduced lid mobility exacerbated by the tendency for the lax upper lids to override the lower lid and abrade the lashes. The ultrastructural findings in the eyelids of patients with pachydermoperiostosis have not been previously reported. There appear to be no specific features indicative of the disease. The finding of basal lamina reduplication round the dermal blood vessels has also been described in the skin from other sites in pachydermoperiostosis.[13] It is, however, a completely non-specific feature which has been described in a wide variety of conditions such as telangiectasia, lipid proteinosis, diabetes, and porphyria.[14]

We believe that the deposition of dermal mucin seen in this case and reported elsewhere, together with the inherited nature of the disease, suggests that pachydermoperiostosis could be classified among the group of primary cutaneous mucinoses. This group of connective tissue disorders shows deposition of fibroblast derived mucin in the dermis, which may be focal or diffuse and is often associated with other systemic abnormalities. These diseases show a common mucin deposition which is a glycosaminoglycan consisting of hyaluronic acid bound to small amounts of chondroitin sulphate and heparin. This is in contrast to the storage diseases, Hunter's and Hurler's syndromes, where the predominant mucin is chondroitin sulphate alone. Examples of the primary cutaneous mucinoses include myxoedema, pretibial myxoedema, and lichen myxoedematosus, in which the common histopathological features include mucin deposition in the dermis together with variable numbers of stellate fibroblasts and a perivascular chronic inflammatory cell infiltrate.[15] The mucin characteristics and the histology in pachydermoperiostosis appear to be similar. To clarify the situation further it might be of benefit to perform fibroblast culture studies and more precise glycosaminoglycan analyses.

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# LETTERS TO THE EDITOR

## Beam obstruction hazard on Q-switched Nd-YAG ophthalmic lasers: a safety device for the Nanolas laser

SIR,—Short pulsed neodymium-YAG lasers are now commonly employed for a wide range of outpatient ophthalmic procedures,[1] and some important safety aspects have been considered elsewhere.[2 3] We have recently identified a further potential hazard which applies to the Nanolas Ophthalmic Laser System manufactured by Biophysic Medical SA.

The problem is that the slit-lamp lighting system can be positioned by the operator in such a way that it partially obstructs the laser beam. As far as the operator is concerned this is manifested solely by a slight diminution in intensity of part of the aiming beam system, and it may not be noticed because the operator's attention is primarily directed towards focusing on the structure to receive treatment. When the laser is fired under these conditions, photo disruption may not occur and the operator is liable to increase the power level to produce the desired effect. Thereafter, should the operator move the slit-lamp illumination system so that it no longer obstructs the laser beam, excessive power levels may be delivered to the eye, with predictable adverse consequences.

To prevent this situation from arising we have developed a safety system which prevents the YAG laser from being fired if the slit-lamp is within the region where it could mask the laser beam.

### SAFETY SYSTEM

The system which we have developed is illustrated in Figure 1. A housing has been fitted to the main column of the optical system. This contains a series of microswitches which are activated by a collar which is fitted round the barrel of the slit-lamp. As the lighting system is moved into the zone where it obstructs the laser beam, the collar depresses a trigger bar on the housing, which in turn operates one of the safety system microswitches. This prevents the laser from being operated. The safety switches are 'closed' under the 'no danger' condition. Hence any break in the additional wiring will cause the system to fail safe.

### DISCUSSION

The safety system described does not interfere in any way with either the slit-lamp or the optical or delivery systems. It is very easily fitted and requires only a small amount of additional wiring. No engineering work is required on the actual machine apart from drilling a hole to take an electrical socket. One of the criteria which had to be met by this system was that it should not pose any restriction on the movement or position of the slit-lamp, so that the slit-lamp may be used independently of the laser, and that it should prevent the firing of the YAG laser only if the illumination system entered the exclusion zone. An alternative to a cut-out switch would be an alarm which could sound either when the slit-lamp is in the exclusion zone or when the 'fire' button is depressed. We believe that this hazard is not confined to the Nanolas system, and other YAG units in which the height of the slit lamp can be adjusted could have a similar problem.

We thank Mr I Smith of the Photographic Department at the Glasgow Eye Infirmary for the illustration and the staff of the Workshops at the Department of Clinical Physics and Bioengineering who manufactured and fitted the safety system.

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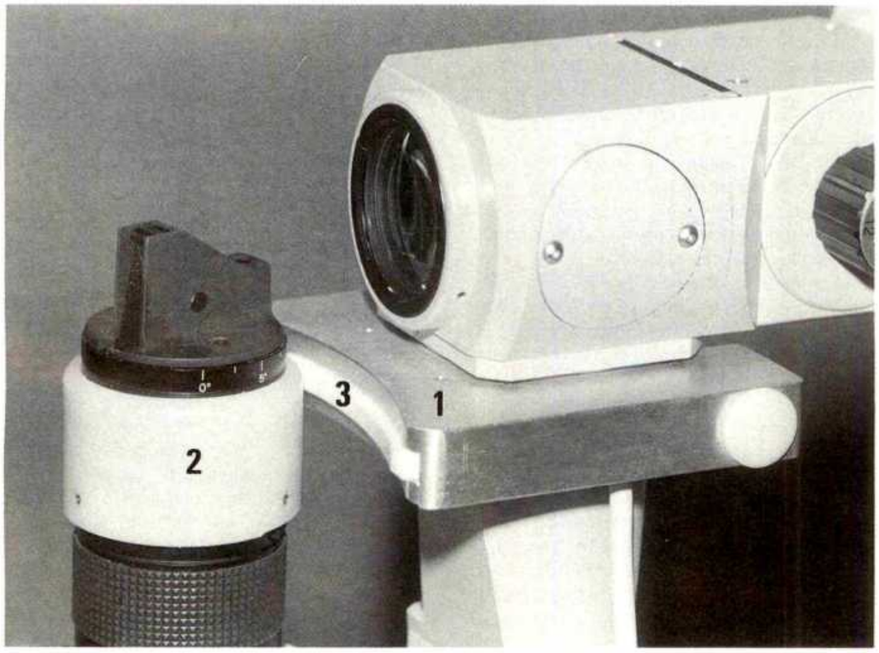

*Figure 1 Safety system fitted to Nanolas ophthalmic laser. 1. Microswitch housing. 2. Collar on slit-lamp barrel. 3. Microswitch trigger bar.*

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## Practical hazards of photic sneezing

SIR,—Even trivial symptoms are more easily tolerated if you can put a name to them, even if that produces only an illusory understanding of their significance. I was therefore very pleased to come across the recent paper[1] and editorial[2] about photic sneezing, for I've suffered from this problem for over 20 years in ignorance of its label and believing that I was unique in my suffering. Your statement[2] that it occurs in 'normal people' is especially welcome.

Photic sneezing has two hazards not mentioned in either of these publications. The first is the potentially dangerous sneezing which can occur while driving a car on a sunny day. I find that sudden exposure to sunlight when emerging from a road tunnel of sufficient length is sure to induce a sneeze, with accompanying momentary blindness. Driving under motorway bridges is no problem, because I'm not in the gloom for long enough, but driving through sunlit gaps in otherwise dense forest or past blocks of buildings can bring on a sneeze. Even driving past those long roadside stands of poplars so characteristic of northern France can cause a sufficient change in the level of light.

The second hazard is more personal, being that paroxysmal hypertension induced when people who observe my photic sneezing make solicitous mutterings about my 'hay fever,' even on the kind of cold clear winter day when the air contains not a single pollen grain. That my problem has a different aetiology and a nice pithy label will simplify explanations wonderfully.

E W BENBOW
*Department of Pathological Sciences,*
*University of Manchester,*
*M13 9PT*

1 Katz B, Melles RB, Swenson MR, Schneider JA. Photic sneeze reflex in nephropathic cystinosis. *Br J Ophthalmol* 1990; **74**: 706–8.
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## Genetic counselling in retinoblastoma

SIR,—In our recently published paper[1] we cited a risk to offspring in the 'Discussion' of 1 in 2. However, we have since been informed by our colleagues in clinical genetics that identification of spontaneously regressed tumours in the grandparents in this case would have given a prior risk of 1 in 2 for their offspring. In the presence of normal retinae their risk would drop to 1 in 11, if the general 90% penetrance figure is used. This, in turn, would mean a risk of close to 1 in 11 for their own child inheriting the mutation, given both parents were potentially 'non-penetrant' carriers. In fact the risk of 1 in 32 given previously was in relation to any recessive disorder (rather than specifically retinoblastoma) given they were first cousins.

JOHN K COWELL
*Molecular Oncology Laboratories,*
*Imperial Cancer Research Fund,*
*London*

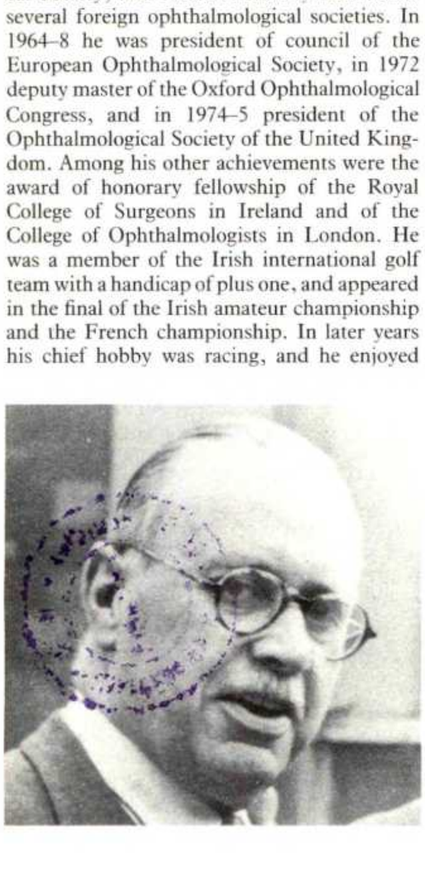
1 Onadim Z, Hykin PG, Hungerford JL, Cowell JK. Genetic counselling in retinoblastoma: importance of ocular fundus examination of first degree relatives and linkage analysis. *Br J Ophthalmol* 1991; **75**: 147–50.

# OBITUARY

## Louis Werner, *MB, BCh, BAO (Dublin), DOMS (Eng), Hon FRCSI*

Doyen of Irish ophthalmology, and past president of the Ophthalmological Society of the United Kingdom and of the Irish Ophthalmological Society, Louis Werner died in Dublin on 6 March 1991 in his 90th year. His grandfather left Alsace when it became part of Germany after the Franco-Prussian war and was commissioned as a portrait painter in Ireland. His father, also Louis Werner, was a gold medallist in philosophy and devoted his career to ophthalmology in Dublin, where, together with Sir Henry Swanzy, a past president of the Ophthalmological Society of the United Kingdom, he wrote a standard textbook on diseases of the eye which greatly raised the status of Irish ophthalmology. The son's planned education at Oundle was abandoned when *SS Leinster* was torpedoed, with loss of life of boys returning to school, and continued at St Stephen's Green School, Dublin, where young Louis excelled at rugger, cricket, and tennis on his way to second place in the entrance examination to Trinity College, Dublin. He was awarded the anatomy prize and first class honours and first place in medicine, being placed second with honours in surgery.

After qualification he worked under Sir John Parsons at Moorfields for a year and soon after was appointed surgeon to the Royal Victoria Eye and Ear Hospital and four other hospitals in Dublin. He was lecturer in ophthalmology, Dublin University, and examiner at the Royal College of Surgeons in Ireland, Queen's University, Belfast, and Dublin University. He was Montgomery lecturer in 1932 at the age of 31, twice president of the Irish Ophthalmological Society, and elected honorary member of several foreign ophthalmological societies. In 1964–8 he was president of council of the European Ophthalmological Society, in 1972 deputy master of the Oxford Ophthalmological Congress, and in 1974–5 president of the Ophthalmological Society of the United Kingdom. Among his other achievements were the award of honorary fellowship of the Royal College of Surgeons in Ireland and of the College of Ophthalmologists in London. He was a member of the Irish international golf team with a handicap of plus one, and appeared in the final of the Irish amateur championship and the French championship. In later years his chief hobby was racing, and he enjoyed many successful visits to the national hunt festival meeting at Cheltenham. In great demand as an after dinner speaker both in the British Isles and abroad for his clear enunciation, Irish wit, and Alsation humour, he brought pleasure to every variety of audience.



Louis was a great teacher and had deep interest in many problems, especially those of glaucoma, and he was one of the first to appreciate the importance of relative pressures within and without capillary walls in the retina and optic nerve. He made many contributions to Irish and British ophthalmology and in his fluent French read papers in Paris and Alsace. He carried a heavy burden of responsibility but continued to work courageously in spite of pain, poor vision, and restricted mobility until almost the end of his life. He married first Mary Boyd Auld, a Scottish lady of great charm and ability who, sadly, died young. In 1950 he married Patricia née MacGillycuddy, widow of Captain George Cordy-Simpson. They had a son Nigel, and his first grandchild Christopher was born four weeks before Louis died. He also had a stepdaughter Janet.

By the Americans Louis wil be remembered as one who, with Becher Somerville-Large and Alan Mooney, restored Irish ophthalmology to its rightful place after the war; to the Irish as their father figure who encouraged the young and set the standard for all; and to the British as the epitome of an Irish colleague, as a delightful friend and the most generous of hosts. Louis had that inborn gift, never to be acquired, which brings out the very best in everyone. He was a fine ophthalmic surgeon and a great gentleman.

HR

# BOOK REVIEW

**Acute Hemorrhagic Conjunctivitis: Etiology, Epidemiology and Clinical Manifestations.** Eds Y Uchida, K Ishii, K Miyamura, S Yamazaki. Pp 438. £133.40. Karger: London. 1989.

About 20 years ago ophthalmic communities witnessed the birth of acute haemorrhagic conjunctivitis (AHC) in Africa. Since then the infection has spread to other continents, affecting hundreds of millions of people.

AHC is an acute and highly contagious infection. It differs from other viral or bacterial conjunctivitis by its short incubation period of about 24 hours, short clinical course of about one week, and its association with severe subconjunctival haemorrhages. The conjunctivitis was first identified on 26 June 1969 in a suburb of Accra, the capital of Ghana. In three months it spread to all parts of Ghana and from there to the west, north, and eastern parts of Africa. In the next two years pandemics of AHC appeared in Asia and the Far East, affecting tens of millions of people. A second pandemic of AHC developed 10 years after the first, affecting Oceania and North, Central, and South America in addition to Africa and Asia. Between the pandemics the AHC remained endemic in overpopulated areas with a hot and humid climate, causing sporadic cases as well as small outbreaks. Several small outbreaks of AHC, mainly in hospitals, have been reported from some European countries.

Virological studies identified enterovirus 70 (EV70) as the cause of AHC. However, later studies showed that in South-east Asia a coxsackie virus A24 variant (CA24V) is responsible for AHC in addition to EV70.

The articles included in this book are by over 50 authors who have been closely involved in studies of AHC in various countries. The articles are grouped under four chapters. The first chapter reviews the historical background and epidemiological features of AHC. The second discusses the major clinical signs and forms of AHC caused by EV70 and CA24V. The laboratory section (chapter 3) presents the development and values of various virus detection tests and serological tests for the diagnosis of AHC. In the last chapter the authors discuss the results of studies using modern molecular technology for identifying the origin of EV70 and CA24V and their continuing evolution in many parts of the world.

S DAROUGAR

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⁂ All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MASTERCARD, VISA or AMERICAN EXPRESS), stating card number, expiry date and your full name.

# NOTES

### Honorary Fellow

Professor Barrie Jones has received the rare distinction of being elected an Honorary Fellow of the Royal Society of Medicine.

### Infectious diseases congress: change of venue

The German Ophthalmological Society will hold an international symposium, 'Update on infectious diseases of the eye,' on 19–21 September 1991, at Münster (not at Bonn/Cologne, as previously arranged). Further details from: Kongress Sekretariat, CCM Cologne Management, Postfach 18 01 80, Schildergasse 101a, D-5000 Köln 1, Germany.

### Plastic surgery

The 22nd Annual Scientific Symposium of the American Society of Ophthalmic Plastic and Reconstructive Surgery will be held at Anaheim Marriott, in Anaheim, California, on 12 October 1991. Further details from: John M Harrington, MD, 2811 Lemmon Avenue East, Suite 302, Dallas, TX 75204, USA.

### Intraocular inflammation

The 2nd International Symposium on Recent Developments in the Immunopathology of Intraocular Inflammation will take place on 22–25 October 1991 in the University of Aberdeen, Scotland, at the new Maxwell Conference Centre. It will include topics on clinical aspects, experimental models, immunoregulation, accessory molecules, and immunointervention. Further details from: Professor J V Forrester, Department of Ophthalmology, University of Aberdeen, Medical School, Foresterhill, Aberdeen AB9 2DY.

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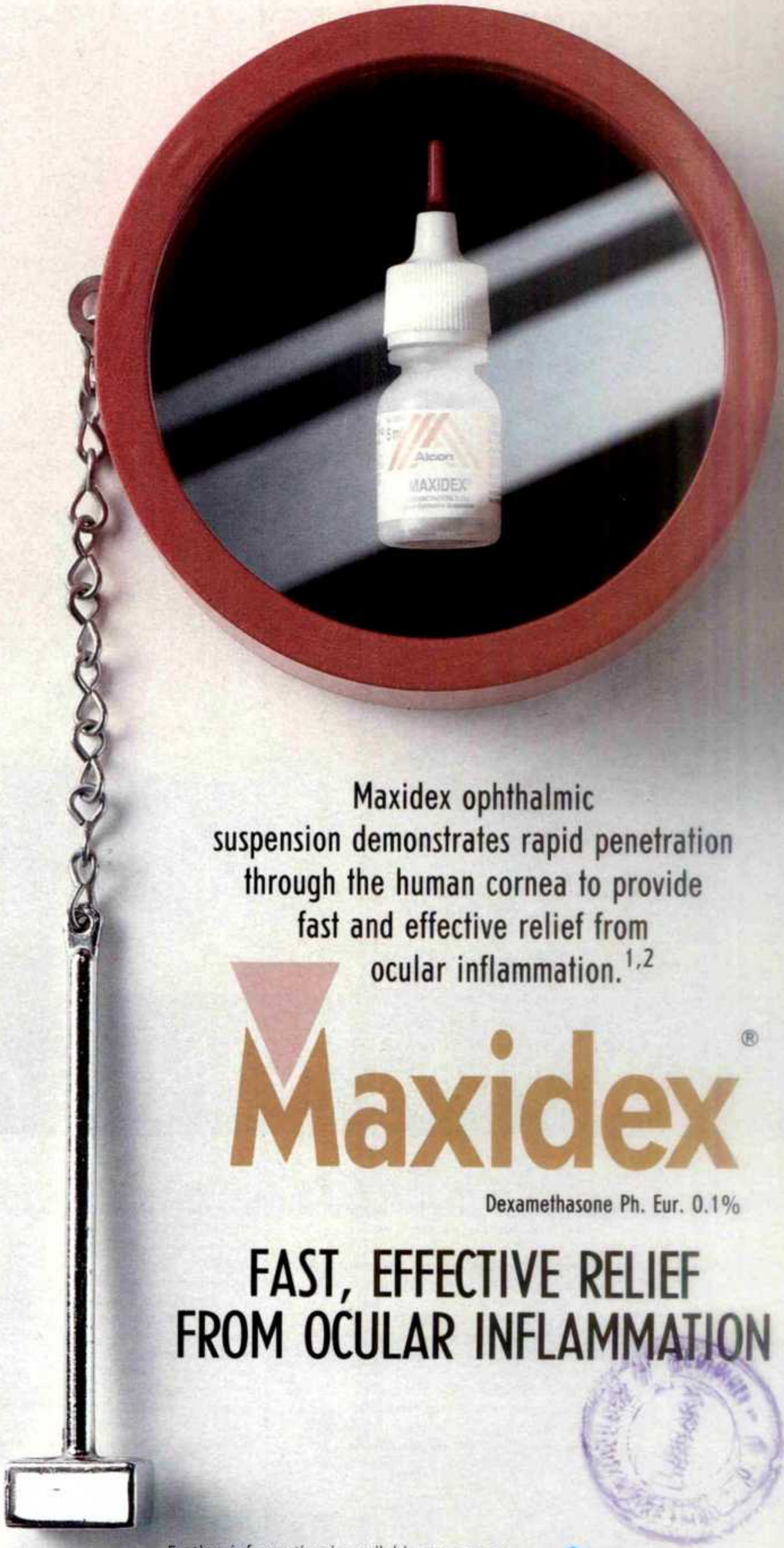

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'Timoptol' may cause side effects of systemic beta-blockade.

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Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blocke should be withdrawn gradually.

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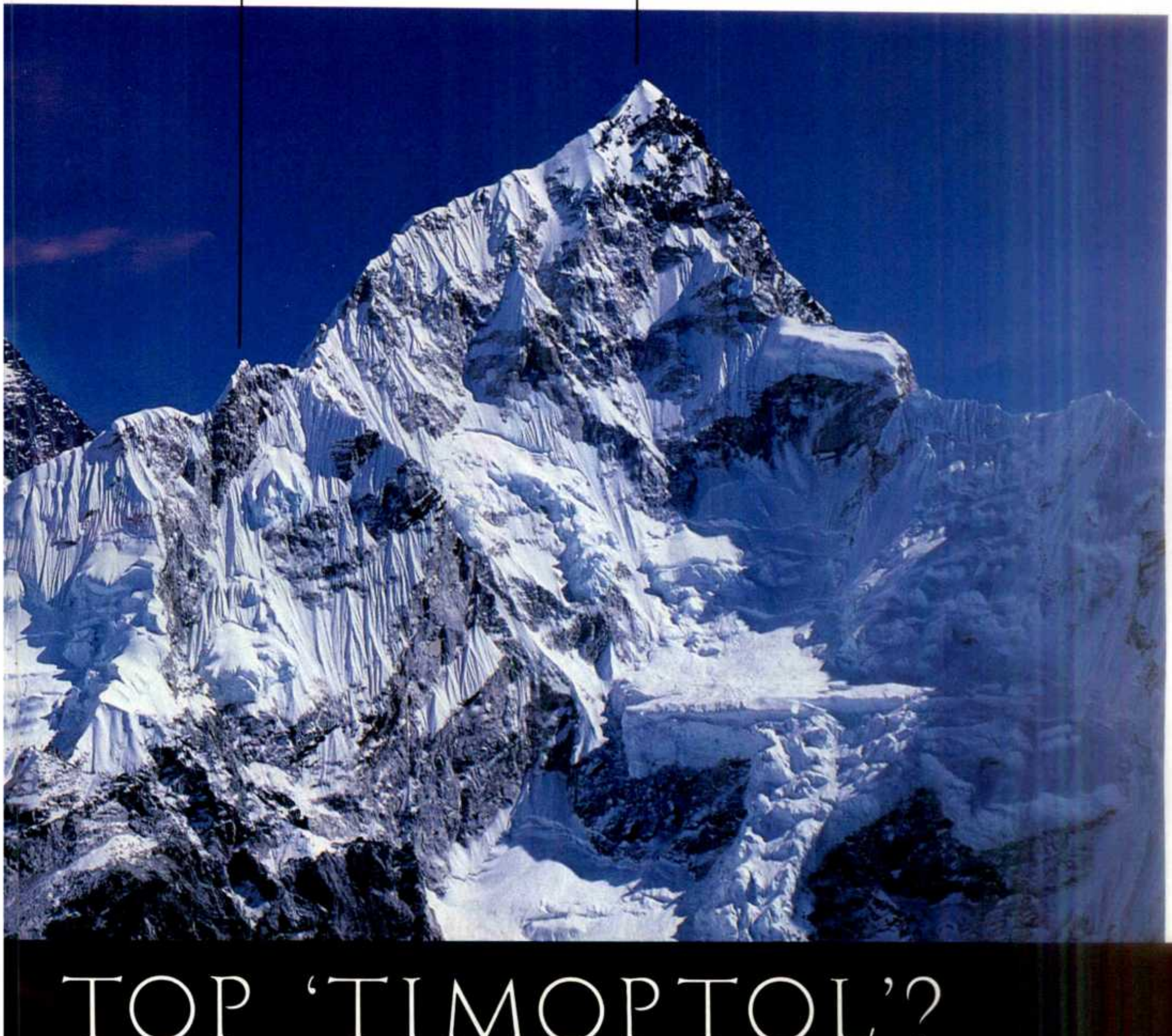

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British Journal of Ophthalmology, 1991, 75, 449

BRITISH JOURNAL OF
OPHTHALMOLOGY

## *Editorial*

# Acute retinal necrosis

This condition, first described in 1971,[1] is characterised by acute full-thickness retinal necrosis associated with a retinal arteritis, which results in retinal destruction. Classically it is seen in healthy persons of any age and either sex, and there is evidence to suggest a viral aetiology.

Viruses implicated in the pathogenesis include varicella zoster, herpes simplex, cytomegalovirus, and Epstein-Barr. Why these viruses, which have been around for a long time, are causing a new disease in man is unknown, but mutant strains are not considered a likely cause.[2] Acute necrotising retinitis showing many features in common with acute retinal necrosis has been reported in immunocompromised patients such as with AIDS or lymphoma.[3] It is not known whether the aetiology is more diverse in this group of patients.

Clinically the eye is inflamed with an anterior uveitis and a marked vitritis. The necrotic lesions in the retina appear white and may be peripheral or patchy over the entire fundus. The lesions tend to coalesce, and the vitreous becomes very cloudy owing to the necrotic debris falling off the retina. The view of the fundus may become obscured, and examination of the retina by ultrasound can then become necessary to detect subsequent detachment. The affected retina becomes destroyed and, when healed, is thinned and atrophic. The extent of the disease may vary. Some patients have small lesions confined to the periphery and subsequently can have a good visual prognosis. In others most of the retina may become involved, and obviously visual prognosis deteriorates with posterior pole involvement.

In 36% of cases the second eye becomes involved, usually within six weeks of the onset of disease in the first eye, but longer time intervals – up to 11 years – have been reported. About 75% of eyes develop rhegmatogenous retinal detachments within one to two months of disease onset, with multiple holes occurring in the thinned atrophic retina. Profound visual loss can also occur as a result of ischaemic optic neuropathy due to thrombotic arteriolar occlusion and infiltration of the optic nerve by inflammatory cells.[4] No viral particles have yet been identified in the vascular endothelium, in either the retina or optic nerve. The retinal destruction may occur as a result of direct lytic viral infection or from the accompanying obliterative vasculitis, choroidal inflammation, and occlusion.

The mainstay of treatment in the acute phase is with systemic acyclovir therapy, since this drug has a potent antiviral action against varicella zoster, herpes simplex, and Epstein-Barr viruses, the commonest viruses to be implicated in the pathogenesis of this disease.[5] The dose of acyclovir recommended is that which is required for a 50% reduction in virus plaques in tissue culture ($ED_{50}$). Oral acyclovir results in subtherapeutic serum levels, whereas intravenous administration gives levels in the vitreous three times the $ED_{50}$. The main aim of this is to eradicate any existing virus and so prevent new lesions from developing, existing lesions from extending, and second eye involvement if this has not already occurred.

The use of steroids is more controversial. Steroids are indicated for ischaemic optic neuropathy and for other severe inflammatory sequelae such as scleritis, but only after intravenous antiviral therapy has been begun.

Matsuo, Morimoto, and Matsuo in a paper in this issue of the *BJO* report they found no relationship between the final visual outcome and the type of virus found, presence of inflammatory signs, sex of the patient, or, depressingly enough, the early initiation of intensive therapy. This is certainly our experience also. Patients who did badly were over 50 years old and presented with extensive retinal disease. The question the authors raise is whether, if one can identify the patients who will do badly, it would be possible to treat these patients more constructively. Apart from early initiation of maximal antiviral and steroid therapy, one wonders whether they are suggesting prophylactic surgery for retinal detachment. Prophylactic local laser treatment has been found to be unhelpful in limiting the area of retinal necrosis. Many of these patients who do develop a rhegmatogenous retinal detachment require a vitrectomy procedure with silicone oil tamponade as well as scleral buckling. Prophylactic scleral buckling alone is unlikely to be successful, and vitrectomy plus silicone oil in an inflamed eye as a prophylactic therapy is unlikely to be realistic. Consideration could be given to prophylactic vitrectomy with 360° endolaser photocoagulation to patients in the high risk group. Prophylactic scleral buckling with intravitreal acyclovir was carried out successfully in two patients with acute retinal necrosis, but whether they would have had a successful outcome anyway is of course unknown.[6]

Given that patients will present to us with established disease, future more effective treatment is likely to rest on a greater understanding of the pathogenesis of the retinal inflammation and destruction, better antiviral drugs, and appropriate manipulation of the immune system.[6]

SUSAN LIGHTMAN

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British Journal of Ophthalmology, 1991, 75, 450–454

ORIGINAL ARTICLES

# Factors associated with poor visual outcome in acute retinal necrosis

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## Abstract

**We reviewed 22 consecutive patients (26 eyes) with acute retinal necrosis to elucidate whether there was any sign at an early stage to predict poor visual outcome. Final visual acuity of the patients fell into two groups, one worse than 20/600 (15 eyes) and the other better than 20/30 (11 eyes). The patients with poor visual outcome showed diffuse retinal arteritis or arterial obliteration which was associated with reduced amplitude of electroretinographic a and b waves and elevated levels of circulating immune complex, even at an early stage when retinal exudates were still localised to the peripheral fundus. The retinal exudates in these patients extended rapidly to the posterior pole. In contrast, the patients with good visual outcome showed retinal arteritis limited within retinal exudates throughout the course. These signs at an early stage can be used as prognostic factors to manage patients with acute retinal necrosis more constructively.**

In acute retinal necrosis isolated exudates occurring initially in the peripheral retina become confluent and extend to the posterior pole. The retinal exudates are usually associated with retinal vasculitis in varying degrees and anterior segment inflammation.[1-5] Most patients with acute retinal necrosis have a poor visual outcome due to traction or rhegmatogenous retinal detachment. Recently, we proposed a mild type of acute retinal necrosis which took a self-limiting course and had good visual outcome.[6] If we can predict whether a given patient with acute retinal necrosis on his/her initial visit will take a fulminant course or not, we can manage the patient more constructively. To this end we reviewed patients with acute retinal necrosis to elucidate the following two points: (1) Which clinical characteristics are associated directly with poor visual outcome? (2) Is there any sign on initial visit to predict poor visual outcome?

## Patients and methods

We reviewed 22 consecutive patients (26 eyes) with acute retinal necrosis seen in Okayama University Hospital during 1974–89. The six patients reported previously as proposed mild type of acute retinal necrosis[6] were included in the study as well as other unreported patients. The charts were checked retrospectively for the following items: age, sex, laterality, year and month of onset, place of onset, initial signs, examinations on initial visit, pathogenic virus, and clinical course. Information on initial signs checked included aqueous cells, mutton fat keratic precipitates, intraocular pressure, the extent of retinal arteritis and phlebitis, and retinal area of involvement with exudates. Special examinations checked were amplitude of electroretinographic a and b waves, erythrocyte sedimentation rate, and levels of circulating immune complex (determined by C1q binding assay), c-reactive protein, and serum IgG. Electroretinographic amplitude was expressed as the ratio of the amplitude between an affected eye and a fellow eye in unilateral involvement, and, in cases of bilateral involvement, as the ratio between the amplitude of an affected eye and the mean amplitude of all the unaffected eyes. Findings checked in the clinical course were speed of retinal exudate extension, final retinal area involved with exudates, final location to which retinal exudates extended, and development of vitreoretinal adhesions.

The areas of retinal exudates on the initial visit and on the day when the exudates stopped extending were estimated roughly from fundus charts and/or panoramic fundus photographs and expressed as a percentage of total retinal area. The extending area of retinal exudates was denoted by subtracting the area of retinal exudates on the initial visit from the area on the day when retinal exudates stopped extending. The speed of extension of retinal exudates was calculated by dividing the extending area of retinal exudates by days required for extension – that is, days from initial visit to the day when exudates ceased extending. How posteriorly retinal exudates reached was expressed as follows: (I) exudates were restricted to the area between the ora serrata and vortex veins; (II) exudates extended into the area between vortex veins and vascular arcades; (III) exudates extended further beyond vascular arcades. Group II was divided further into IIt, where exudates involved the whole 360° of area II and IIp, where exudates involved partial degrees of area II.

Retinal arteritis in this study included sheathing of retinal arteries observed by ophthalmoscopy, arterial obliteration, or dye leakage from retinal arteries demonstrated by fluorescein angiography. Retinal phlebitis indicated perivenous haemorrhage, sheathing, or dye leakage. The extent of retinal arteritis and phlebitis was expressed as those limited within retinal exudates or those observed diffusely from the optic disc. Vitreoretinal adhesion was confirmed echographically or by Goldmann's three-mirror examination.

Pathogenic virus was determined on the basis of (1) more than four times increase in aqueous titre to virus in convalescent phase compared with that in acute phase; (2) markedly raised titre in vitreous fluid obtained in vitrectomy; (3) significant ratio of aqueous antibody titre to serum antibody titre corrected by each IgG level.

All the patients were given a large dose of steroid (usually a drip infusion of prednisolone tapered from 200 mg daily dose) combined or uncombined with acyclovir. Before the introduction of acyclovir to clinical practice a steroid had been given in combination with aspirin, plasma exchange, and other measures. We have recently used the maximum dosage of acyclovir, namely, 1500 mg/day for two-four weeks, while previously we had used rather smaller doses, 500-750 mg/day, when acyclovir had just been introduced. The patients in this study underwent surgical treatment such as scleral buckling, vitrectomy, gas tamponade, or silicone tamponade only when they developed retinal detachment. Neither prophylactic surgery nor laser photocoagulation was performed. In order to examine the therapeutic effect the final visual acuity was plotted against the daily dose of acyclovir and the duration of the disease from its onset (record of symptom) to the day when the above-mentioned therapy was started.

## Results

The age of the 22 patients (11 male and 11 female) ranged from 21 to 85. Four patients had involvement of both eyes and 18 patients unilateral involvement (in 10 patients the right eye and in eight patients the left eye). The patients fell into two groups, those (11 eyes) with final visual acuity better than 20/30 and those (15 eyes) with final visual acuity worse than 20/600 (Figure 1). Thirteen eyes out of 15 with poor visual outcome developed rhegmatogenous and/ or traction retinal detachment, while the other two showed macular involvement with exudates. The patients older than 50 years had a poor visual outcome (Fisher's exact probability test,

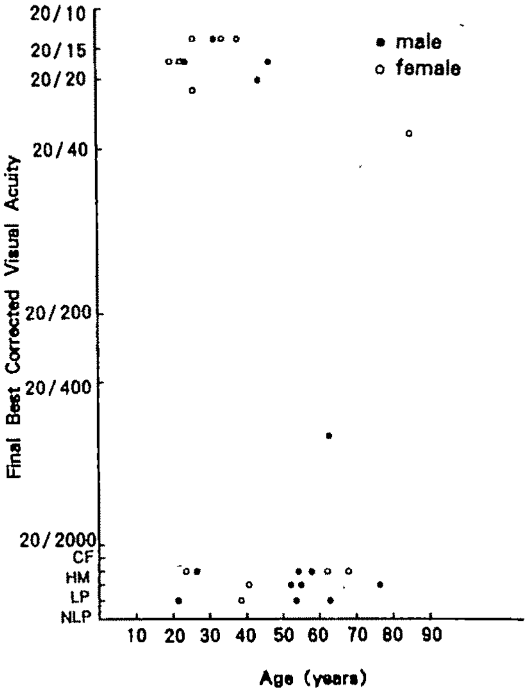

*Figure 1 Patients fall into two groups: those with good visual outcome and those with poor visual outcome. Patients older than 50 years have significantly poor visual outcome.*

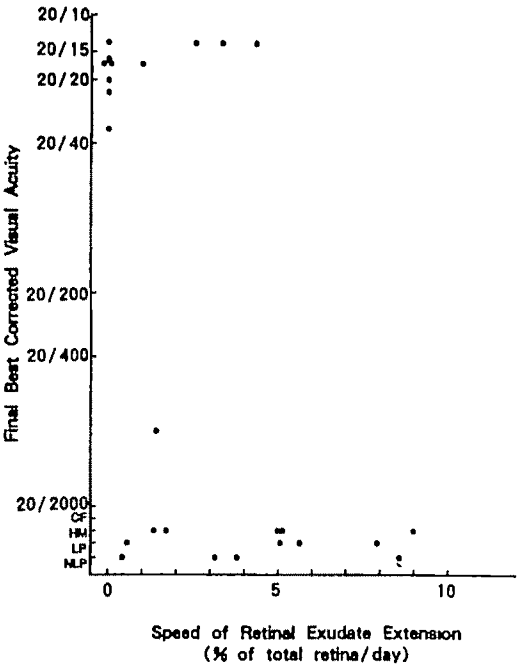

*Figure 2 Retinal exudates extend rapidly in patients with poor visual outcome, but slowly in those with good visual outcome.*

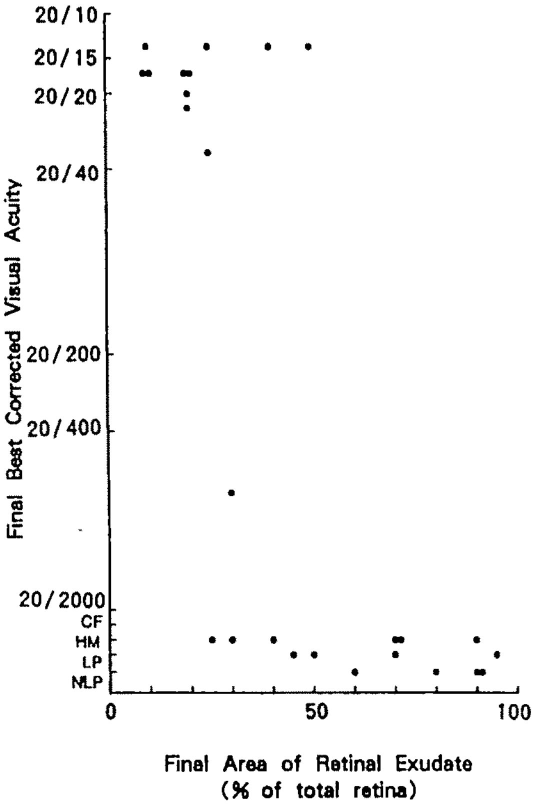

*Figure 3 Final retinal area involved with exudates is large in patients with poor visual outcome, but small in patients with good visual outcome.*

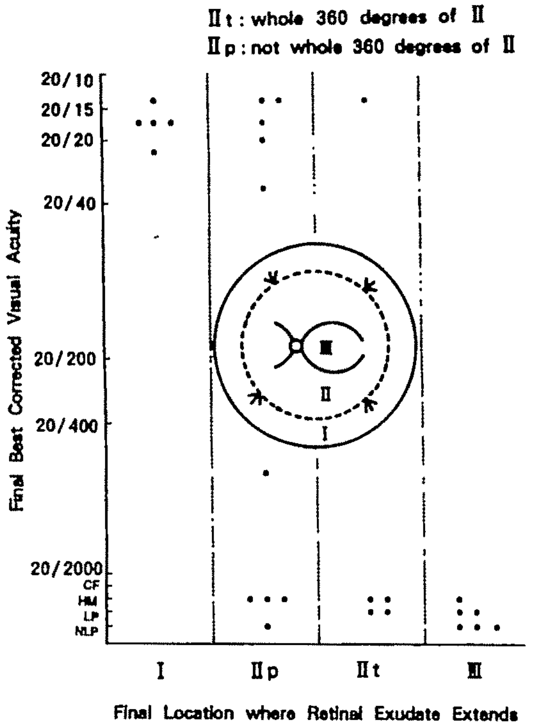

*Figure 4 Retinal exudates extend to posterior pole in patients with poor visual outcome.*

$p<0{\cdot}01$). There was no sex difference between those with good and poor visual outcome.

The speed of extension of retinal exudate was significantly faster in patients with poor visual outcome (mean, 10% of total retina/day) than in those with good visual outcome (mean, 1% of total retina/day) as shown in Figure 2 (a significant difference by Fisher's exact probability test, $p<0{\cdot}01$). The final retinal area involved with exudates was large in the group with poor visual outcome (mean, 60% of total retina), and small in the group with good visual outcome (mean, 20%) as shown in Figure 3 (significant difference in Fisher's exact probability test, $p<0{\cdot}005$). The group with poor visual outcome showed a significantly higher rate of posterior pole involvement than did the group with good visual outcome as shown in Figure 4 (significant difference by Fisher's exact probability test, $p>0{\cdot}005$). Vitreoretinal adhesion was found in 13 eyes (87%) of the group with poor visual outcome in contrast with one eye (9%) in the group with good visual outcome (significant difference by Fisher's exact probability test, $p<0{\cdot}005$).

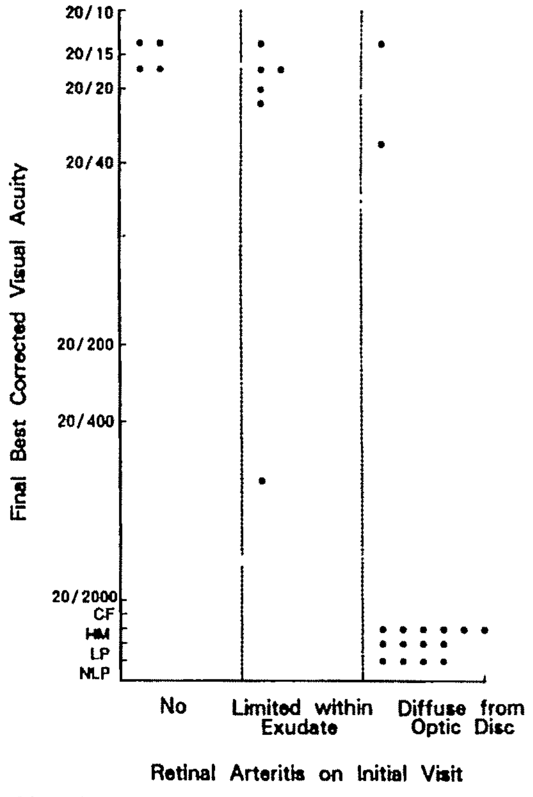

*Figure 5 Patients with poor visual outcome show diffuse retinal arteritis even on initial examination.*

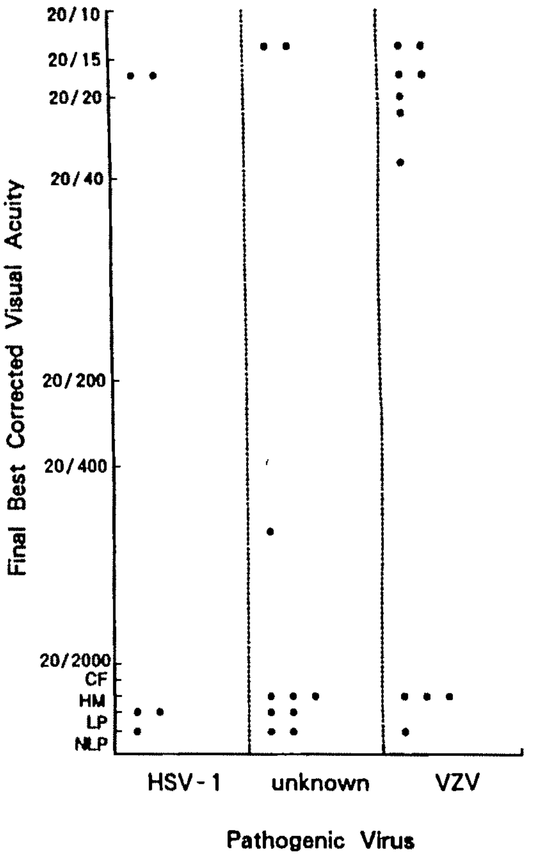

*Figure 6 There is no relationship between pathogenic virus and visual outcome. VZV=varicella zoster virus.*

The visual outcome was poor in the 14 patients out of 16 who showed retinal arteritis diffusely from the optic disc even on initial examination when retinal exudates were still localised to the peripheral fundus (Fig 5). In contrast, the visual outcome was good in the nine patients out of 10 who showed retinal arteritis limited within the exudates or no apparent arteritis on initial examination (significant difference by Fisher's exact probability test, $p<0{\cdot}01$). The retinal phlebitis was limited within retinal exudates in every patient regardless of the poor or good visual outcome.

The amplitude of electroretinographic A wave on initial examination was significantly high in the group with good visual outcome (mean of affected eye/unaffected eye ratio 0·73 range 0·5–0·98), compared with that in the group with poor visual outcome (mean of the ratio 0·28, range 0–0·5) (significant difference in Student's $t$ test, $p<0{\cdot}05$). The same tendency was also found in the amplitude of electroretinograph b wave.

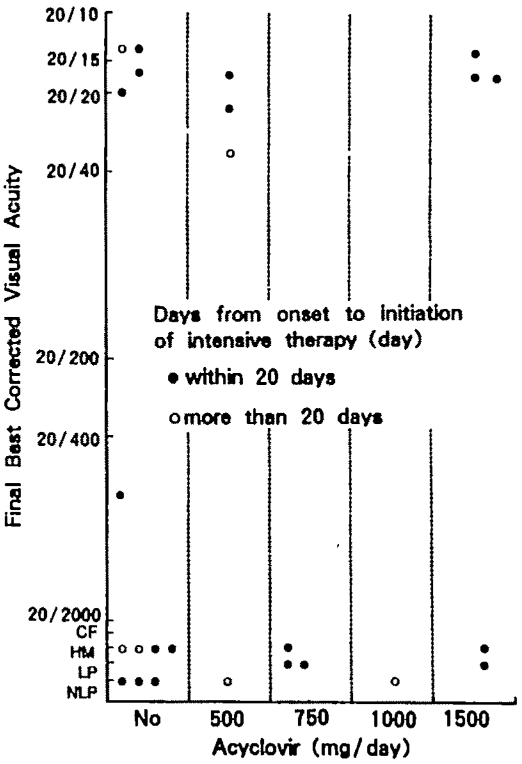

*Figure 7 Maximum dose of acyclovir does not necessarily lead to good visual outcome.*

The levels of circulating immune complex on initial examination were higher in the group with poor visual outcome (mean 4·3 mg/l, range 1·4–7·6 mg/l) than in the good visual outcome group (mean 3·0 mg/l, range 1·0–6·4 mg/l), though the difference was not statistically significant.

What were the causes of the reduced amplitude of electroretinographic waves on initial examination? A large retinal area of involvement with exudates was naturally accompanied by reduced electroretinographic amplitude, but it should be noted that there were a group of patients showing the low amplitude in spite of limited area of retinal exudates. Such a low amplitude of the electroretinographic waves in these patients could be attributed to retinal arteritis spreading diffusely from the optic disc, from the following results: the retinal arteritis spreading diffusely from the optic disc was associated with the lower amplitude of electroretinographic a wave (mean of affected eye/unaffected eye ratio 0·29, range 0–0·5), while no retinal arteritis or arteritis limited within the exudates was associated with the higher amplitude (mean of the ratio 0·84, range 0·7–0·98) (significant difference by student's $t$ test, $p<0.01$). Furthermore, the levels of circulating immune complex were higher in the patients with retinal arteritis spreading diffusely from the optic disc (mean 4·3 mg/l, range 1·4–7·6 mg/l) than in the patients with no arteritis limited within the exudates (mean 3·0 mg/l, range 1·0–6·4 mg/l), though the difference was not statistically significant.

Factors which had no relationship with final visual acuity were pathogenic virus (Fig 6), sex difference, place of onset year and month of onset, such signs on the initial visit as the extent of aqueous inflammatory cells, presence of mutton fat keratic precipitates, and intraocular pressure, and such examinations on the initial visit as levels of c-reactive protein and serum IgG, and erythrocyte sedimentation rate.

To examine the effect of acyclovir the final visual acuity was plotted against the daily dose of acyclovir (Fig 7). Large doses of acyclovir could not stop the extension of retinal exudates, which led to poor visual outcome, while there were patients who had good visual outcome without the administration of acyclovir. Figure 8 shows the effect of early therapy on final visual outcome. Early initiation of intensive therapy did not necessarily lead to good visual outcome.

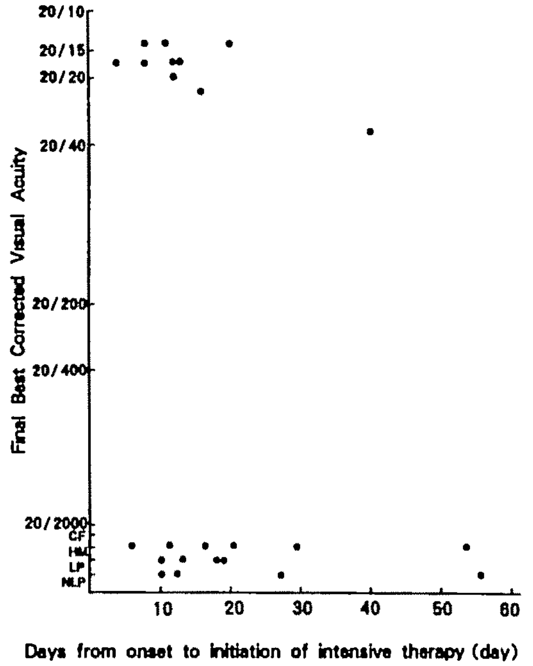

*Figure 8 Initiation of treatment in an early phase of the disease does not necessarily lead to a good visual outcome. CF=counting fingers. HM=hand movements. LP=light perception. NLP=no light perception.*

## Discussion

In the patients with poor visual outcome the retinal exudates extended rapidly, involved large areas of the retina, including the posterior pole, and developed vitreoretinal adhesion at a high rate, as opposed to the patients with a good visual outcome. Direct causes of poor visual acuity were traction and/or rhegmatogenous retinal detachment and macular involvement, with exudates resulting from above characteristics.

It should be noted that retinal arteritis (sheathing, fluorescein dye leakage, and/or arterial obliteration) was diffuse from the optic disc in the patients with poor visual outcome even on initial examination when retinal exudates were still localised to the peripheral fundus. In contrast, the patients with good visual outcome showed retinal arteritis limited within the exudates throughout the course. The manifestation of diffuse retinal arteritis on initial examination was accompanied by reduced amplitude of electroretinographic a and b waves, and elevated levels of circulating immune complex. Therefore the extent of retinal arteritis, amplitude of electroretinogram, and levels of circulating immune complex at an early stage of acute retinal necrosis can be used as prognostic factors to predict the clinical course and visual outcome.

If we see patients with good prognostic factors, we can treat with ordinary combinations of steroid and acyclovir. But in patients with poor prognostic factors we have to consider, in addition to acyclovir and steroid, prophylactic encircling procedures, laser photocoagulation, or early vitrectomy for vitreoretinal adhesions before they develop retinal detachment.[7,8]

Diffuse retinal arteritis and arterial obliteration could result in large areas of hypoxic retina leading to low amplitude of the electroretinogram. We previously demonstrated that circulating immune complex obtained by plasma exchange in acute retinal necrosis contained herpes virus antigens.[9,10] Elevated levels of circulating immune complex would be either the result or the cause of extensive inflammation in retinal vascular walls. Extensive inflammation with herpes virus and consequent immune response in the retina may release large amounts of immune complex into the circulation, which would further disseminate immune-complex-induced inflammation along the vascular wall of the retina. Conversely, infection of the retinal vascular wall with herpes virus and the following immune response may lead to liberation of a large amount of immune complex into the circulation. In either case the patients with extensive retinal arteritis and high levels of circulating immune complex would have extensive infection with herpes virus and strong immunological reaction by the host. Recently, Forster and associates described two patients, both seropositive for human immunodeficiency virus, who developed retinal necrosis limited to the outer retina and sparing the retinal vasculature during systemic herpes zoster infection.[11] The fact that retinal arteritis was absent in the immunocompromised state, such as that due to the acquired immunodeficiency syndrome, suggests further that the immune response plays an important role in causing the retinal arteritis usually observed in acute retinal necrosis occurring in otherwise healthy people.

Initiation of intensive therapy at an early stage of the disease would not necessarily lead to a good visual outcome. Maximum doses of acyclovir combined with steroid will not stop the rapid extension of retinal exudates in some patients, while in other patients retinal exudates extended very slowly with steroid only. These facts support the notion that acute retinal necrosis in itself may have a continuous range of severity varying from mild to fulminant. Since the patients fell into two groups, with good and poor final visual acuity, it is convenient to classify acute retinal necrosis roughly into a fulminant type and a mild type, as we proposed previously.[6] The difference in severity of the disease could be attributed to different virulence of herpes virus and/or different extent of host immune response. Human leucocyte antigens may underlie this varying severity of acute retinal necrosis, which will be described in another report.

The statistical results in this study were obtained from patients who were not treated in exactly the same way. In addition we did not consider other clinical factors, such as the presence of complete posterior vitreous detachment before onset of the disease, which might be important for visual outcome.[6] These factors, if considered, may modify the statistical results, which must await future studies.

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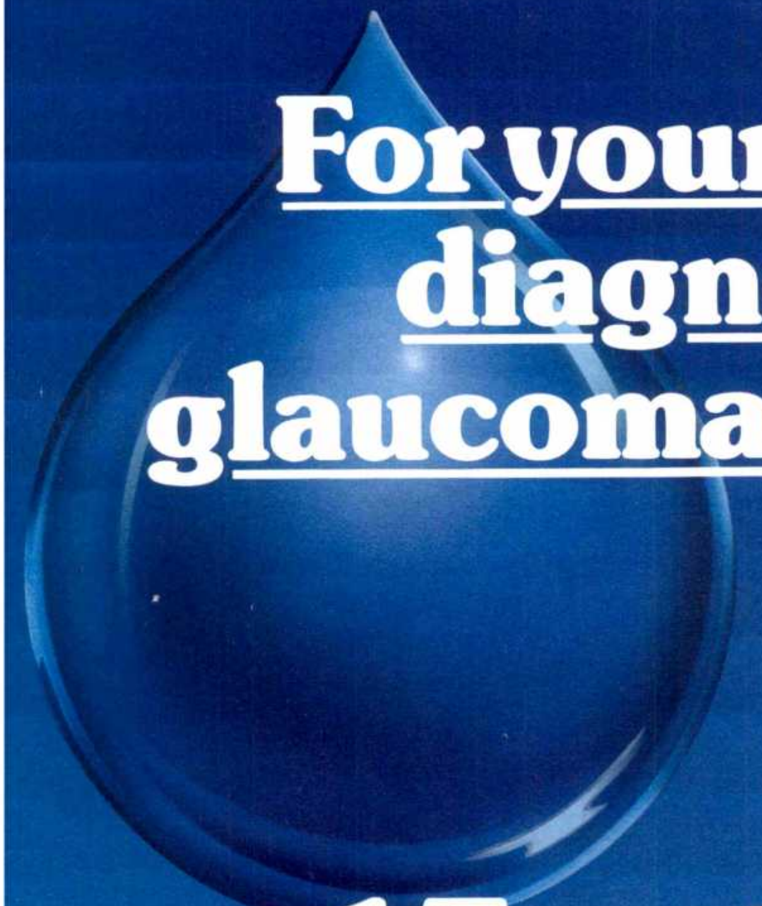

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# Surgical management of retinal detachment associated with the acute retinal necrosis syndrome

H Richard McDonald, Hilel Lewis, Allan E Kreiger, Yossi Sidikaro, John Heckenlively

## Abstract

**We operated on nine eyes in eight patients with retinal detachment associated with acute retinal necrosis (ARN) syndrome. The patients were treated with scleral buckling, vitreoretinal surgery, or a combination of these treatments. Vitrectomised eyes underwent combinations of lensectomy, membrane dissection, scleral buckling, air-fluid exchange, endolaser photocoagulation, cryotherapy, and retinal tamponade with $C_3F_8$ gas or $SF_6$ gas. Macular attachment was achieved in eight (89%) eyes. Vision improved in seven (78%) eyes, of which five (56%) achieved 20/200 or better vision. Three eyes that had received laser treatment posterior to areas of retinitis suffered retinal detachment despite this prophylactic treatment. Poor visual outcome resulted from viral infection of the optic nerve or macular involvement, macular hole formation, macular pucker, or hypotony.**

Acute retinal necrosis (ARN) is a clinically defined syndrome characterised by confluent, peripheral necrotising vaso-occlusive retinitis, arteritis, and vitritis.[1-10] Although this syndrome was first described in healthy individuals, immunocompromised patients may also be affected.[11-13] Herpes viruses have been implicated as causal agents in ARN.[12-23] Retinal detachment is a frequent complication of the syndrome. The incidence of retinal detachment depends on the extent of peripheral retinal involvement and the degree of vitritis. It has been reported to be as high as 85%, despite the efficacy of acyclovir in hastening the resolution of the retinitis.[1 24-29]

Measures for the prevention or treatment of retinal detachment in eyes with ARN have included prophylactic photocoagulation,[9 24 25 30] prophylactic vitrectomy and scleral buckling with acyclovir infusate during the acute phase of the retinitis,[29 31] scleral buckling alone,[32] and pars plana vitrectomy, endolaser photocoagulation, and long-acting retinal tamponade.[24 29 32-34]

We report here our surgical results for retinal detachment associated with the acute retinal necrosis syndrome.

## Patients and methods

Between 1981 and 1988 we operated on nine eyes of eight patients with retinal detachments associated with the acute retinal necrosis syndrome. Five of the eight patients were females, three males; they ranged in age from 16 to 73 years, mean 40·1 years. Follow-up ranged from nine months to five years, mean 18 months.

Seven of the eight patients were treated with acyclovir either before or concurrently with the development of retinal detachment. These patients were also treated with prednisone and aspirin during their time in hospital. In patients who were treated with prophylactic photocoagulation in an attempt to prevent the occurrence of posterior pole retinal detachment, three to six contiguous rows of laser photocoagulation burns were placed posterior to the confluent peripheral retinitis. Retinal detachment developed following large retinal breaks at the border of necrotic retina in seven eyes. One eye had a retinal break within an area of active retinitis (case 2), and one eye developed a break in the uninvolved retina (case 9). Three eyes underwent scleral buckling alone, while six eyes underwent vitreous surgery.

Those patients undergoing vitreoretinal surgery were operated on by the bimanual technique with a posterior infusion port and fibreoptic illumination. Meticulous anterior vitreous base vitrectomy, with 360° scleral depression, was part of each vitrectomy. Epiretinal membranes were dissected from the retinal surface and removed from each of these eyes.

Encircling scleral buckles were placed in all eyes that had vitreous surgery, not to support specific retinal breaks but to relieve peripheral anterior vitreous base contraction that might occur during the postoperative period. Vitrectomised eyes had air-fluid exchange with internal subretinal fluid drainage by means of preexisting breaks or planned retinotomies. Confluent endolaser photocoagulation was used to treat the edge of attached uninfected retina posterior to the peripheral retinitis. Photocoagulation was also applied round all retinotomy sites and over the scleral buckle. Vitreous substitution with sulphur hexafluoride gas (25%), or perfluoropropane gas (20%) was then performed.

## Results

Nine eyes of eight patients underwent surgery for retinal detachment associated with the acute retinal necrosis syndrome (Table 1). Macular reattachment was achieved in eight (89%) of them.

Two of the nine eyes had partial retinal reattachment. One eye with partial retinal attachment developed postoperative epiretinal membranes that detached a quadrant of extramacular retina and puckered the macula. The patient declined further surgery. The other such eye developed anterior retinal detachment due to anterior proliferative vitreoretinopathy, though the posterior retina remained attached.

Vision improved to the 20/200 level in five (56%) of nine eyes. Of the eight eyes in which the retina was reattached one had no light perception because of optic nerve involvement.

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*Table 1 Surgical results in acute retinal necrosis*

| *Case* | *Age* | *Sex* | *Preop laser* | *Preop vision* | *Acyclovir* | *Surgery* | *Postop vision* | *Anatomical result* | *Follow-up* | *Comments* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 27 | F | + | 3/200 | + | L, V, M, AFX, E, SB, $C_3F_8$ | 5/200 | Attached | 24 mths | 1. Developed peripheral RD, then PVR. Previous herpes zoster uveitis in other eye<br>2. Developed macular pucker postop, declined further surgery |
| 2 | 35 | F | – | HM | + | L, V, M, AFX, E, $C_3F_8$, SB | 20/200 | Attached | 12 mths | 1. Active retinitis and RD<br>2. Acyclovir (IV, and infusate 40 µg/ml)<br>3. Giant retinotomies created during surgery<br>4. Hypotony retinopathy, IOP normal 3 mths postop |
| 3 | 36 | M | + | 7/200 | + | V, M, AFX, E, $C_3F_8$, SB<br>SB | 20/160 | Attached | 12 mths | 1. Developed posterior epiretinal membranes and macular hole<br>2. Increased nuclear sclerosis |
| 4 | 73 | F | – | 20/400 | | SB (segmental) | NLP | Attached | 12 mths | 1 Optic nerve involvement caused NLP |
| 5 | 51 | M | – | 20/300 | + | V, C, AFX, SB, $SF_6$ | 20/80 | Attached | 36 mths | 1. Cataract developed, later removed<br>2 Treated before availability of endolaser |
| 6 | 16 | F | – | HM | – | 1 V, SB, C, $SF_6$<br>2. L, V, M, AFX, E, $SF_6$ | 6/200 | Attached | 24 mths | 1. Developed postop ERM, and became redetached<br>2. Postop hypotony associated with anterior PVR |
| 7 | 16 | F | – | 20/25 | + | SB | 20/20 | Attached | 18 mths | 1. OD of case 6<br>2 Encircling scleral buckle for quadrantic RD |
| 8 | 36 | F | – | HM | – | L, V, M, AFX, C, $SF_6$, SB | NLP | Detached | 60 mths | 1. Prior to accepted use of acyclovir<br>2. Had VH due to neovascularisation<br>3. Developed proliferative vitreoretinopathy postoperatively and declined reoperation |
| 9 | 63 | M | + | HM | + | SB | 20/60 | Attached | 9 mths | 1. Break in uninfected retina, outside demarcated area |

V: pars plana vitrectomy. M: membranectomy. L: lensectomy. AFX: air-fluid exchange. E: endolaser photocoagulation. C: cryotherapy. SB: scleral buckle. $C_3F_8$: perfluoropropane gas. $SF_6$: sulphur hexafluoride. S: silicone oil. RD: retinal detachment. PVR: proliferative vitreoretinopathy. PR: pneumatic retinopexy. ERM: epiretinal membranes. VH: vitreous haemorrhage. HM: hand movements. CF: counting fingers. LP: light perception. NLP: no light perception.

Three eyes had preoperative prophylactic laser posterior to the areas of retinitis. In two of these eyes the retina was treated for 360°. In one eye (case 9) the peripheral retinitis did not involve the entire periphery, and laser was placed round the infected retina, extending anteriorly to the ora serrata. Despite the prophylactic laser, the retina in these three eyes became detached, but was successfully reattached with surgery.

## Discussion

Retinal detachment remains a serious complication of the acute retinal necrosis syndrome. As surgical techniques for dealing with complicated retinal detachment have become more refined, the reattachment rate has improved.[1,24,29,31-34] The visual acuity results have not been as satisfactory, though recently Blumenkranz *et al* reported that five of six eyes achieved 20/200 or better vision after successful repair.[32]

In our series the retina was reattached partially or totally in eight (89%) of nine eyes. Of the two eyes with partial attachment one (case 1) developed postoperative epiretinal membrane formation and macular ectopia and the patient refused further surgery. In the third patient (case 6, OS), the entire posterior pole was reattached. Nevertheless, anterior proliferative vitreoretinopathy redetached the periphery and probably played a part in the patient's postoperative hypotony.

Though vision improved in seven (78%) eyes, it did so to 20/200 or better in only five (56%). In three eyes the retina was reattached, yet vision failed to reach the 20/200 level. These eyes were thought to have associated complications that prevented significant visual improvement, including postoperative macular pucker (case 1), optic neuritis, presumed to be secondary to herpes virus (case 4), and hypotony following reoperation for proliferative vitreoretinopathy (case 6, OS).

Several authors have suggested that in eyes with clear enough vitreous to allow laser, prophylactic photocoagulation should be used to demarcate areas of active retinitis in an attempt to decrease the incidence of posterior retinal detachment.[9,24,25,30] In our series three eyes had prophylactic laser treatment but developed posterior retinal detachment. In one of these eyes (case 9) the break developed outside the area of demarcated retina, presumably in uninfected retina. In case 1 proliferative vitreoretinopathy (PVR) developed and tractionally detached the retina away from the lasered area. Case 3 also developed PVR with an associated macular hole that resulted in posterior retinal detachment.

There appears to be a spectrum of disease severity with the acute retinal necrosis syndrome. Some eyes have fulminant disease requiring advanced vitreous microsurgery, while others have only a mild manifestation of the disease.[35] Some eyes with retinal detachment and ARN can be successfully managed with scleral buckling; two were encircled, and one received only a segmental buckle. Scleral buckling, therefore, may be considered a surgical alternative in mild cases with small breaks, quadrantic involvement, and minimal vitritis.[24,33,34] The majority of ARN cases, however, have multiple, large posterior breaks that are best treated with vitreoretinal surgery.

Good anatomical success rates and visual results have been reported with vitrectomy techniques without scleral buckling.[32] In our series six eyes underwent vitrectomy in combination with various adjunctive procedures (Table 1). No eyes underwent vitrectomy without placement of a scleral buckle.

In most patients requiring vitrectomy for retinal detachment with ARN the lens needs to be removed. This allows easy access to the far anterior peripheral vitreous base. If this peripheral vitreous is allowed to remain, it may contract postoperatively and redetach the retina.[32] Placement of an encircling scleral buckle, combined with meticulous vitreous base dissection, may minimise this complication.

In one eye (case 6, OS) anterior retinal detachment and hypotony developed postoperatively, though the posterior retina was attached. In this case the lens was not removed at the time of the second operation. Another reason for removing the lens is the likelihood of developing a cataract with the use of long-acting gas substitutes or silicone oil. In our series two patients (cases 3 and 5) underwent vitrectomy without lensectomy. Both developed cataracts within several months, requiring cataract surgery.

Short-acting ($SF_6$) and long-acting ($C_3F_8$) gases were used as vitreous substitutes for retinal tamponade following retinal reattachment with air-fluid exchange (Table 1).

Hypotony was a postoperative complication in two patients with successful retinal reattachment (cases 2, 6, OS). In case 2 the retina was reattached and the eye had a normal intraocular pressure (IOP) for several weeks. Vision improved to the 20/128 level. The IOP fell to zero over several weeks and the fundus developed chorioretinal folds, retinal striae, and a boggy, thickened appearance. The vision dropped to 9/200. There was no significant intraocular inflammation at this time, nor was there any anterior proliferative response that might have created ciliary body detachment. After injections of retrobulbar steroids over a three-month period, the IOP rose to 10 mm Hg and vision improved to 20/200. The other patient who developed hypotony (case 6, OS) had traction on the ciliary body created by anterior PVR.[36]

Retinal detachment usually occurs after the acute period of retinal necrosis has passed. The infected necrotic retina thins, so that only a fibroglial remnant remains over the disrupted retinal pigment epithelium in many areas. The vitreous develops various degrees of haziness and inflammatory opacification related to the severity and extent of retinitis, and also related to the immune system's ability to mount a response. The subsequent contraction of the vitreous creates traction on the retina, and large retinal breaks usually form at the borders of the involved and uninvolved retina. One of our cases (case 2) developed a retinal detachment during the acute phase of the retinitis. This eye had partial posterior vitreous separation and retinal breaks within the area of active retinitis. Surgery on such eyes is difficult because of the iatrogenic retinal breaks created by removing areas of attached vitreous from necrotic, detached retina.

Because retinal breaks usually occur when the contracting vitreous tears the necrotic, avascular retina, significant vitreous haemorrhage is not common in ARN. Vitreous haemorrhage can occur, however, in association with neovascularisation created by the inflammatory and ischaemic conditions prevalent in ARN.[37, 38] Panretinal photocoagulation to areas of non-necrotic and segmentally non-perfused retina has been shown to cause regression of optic nerve neovascular proliferation.[39] One eye in our series (case 8) had retinal detachment and vitreous haemorrhage caused by neovascularisation. At the time of surgery the retina behind the vitreous haemorrhage was found to be totally necrotic. Postoperatively the retina became detached again and the eye was eventually enucleated. This patient's other eye also had ARN and disc neovascularisation that responded well to panretinal photocoagulation.

The acute retinal necrosis syndrome may be complicated by retinal detachment. For those eyes with small or single breaks and quadrantic detachments, scleral buckling may be sufficient to reattach the retina. If complicated retinal detachment is present, including those cases with epiretinal membrane formation, marked vitritis, active retinitis, macular hole, or multiple large posterior tears, then pars plana vitrectomy, endolaser photocoagulation, and long acting retinal tamponade have a good chance of reattaching the retina. The visual recovery in these successfully reattached eyes depends on viral infection of the optic nerve, hypotony, macular hole formation, and postoperative epiretinal membrane formation.

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# Neovascular response in ischaemic central retinal vein occlusion after panretinal photocoagulation

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## Abstract

**Twenty seven eyes treated for ischaemic central retinal vein occlusion with panretinal photocoagulation were reviewed. Prior to laser therapy anterior segment neovascularisation predominated (17 eyes) over posterior segment involvement (6 eyes). After photocoagulation anterior segment new vessels regressed or did not develop in the majority of cases. However, in five eyes previously absent posterior segment neovascularisation occurred. These results suggest that photocoagulation alters but does not eliminate retinal ischaemia, thus modulating the neovascular response.**

Central retinal vein occlusion (CRVO) may have a devastating effect on vision and may result in chronic macular oedema and ocular neovascularisation, in particular rubeotic glaucoma. CRVOs with a relative absence of retinal ischaemia (about 75% of all CRVOs) have a better prognosis than those with retinal ischaemia (about 25% of all CRVOs).[1] Panretinal photocoagulation (PRP) is now part of the accepted method of treatment for ischaemic CRVO. The aim of PRP is either to prevent neovascularisation or to induce regression of new vessels once they have occurred.

In contrast to the other vasoproliferative retinopathies – diabetic retinopathy, sickle cell retinopathy, and branch retinal vein occlusion – where the emphasis of neovascularisation is in the posterior segment, in ischaemic CRVO the emphasis of new vessel formation is on the iris and in the drainage angle, with posterior segment involvement being less common.[2-5] Previous studies have concentrated on the regression of neovascularisation following panretinal photocoagulation.[6] However, some of our patients had received PRP for ischaemic CRVO and subsequently developed posterior segment neovascularisation. We therefore reviewed a series of eyes treated for ischaemic CRVO with PRP to determine the pattern of the ocular neovascular response in relation to the degree of ischaemia and photocoagulation.

## Materials and methods

We reviewed all eyes treated at St Thomas's Hospital with PRP for ischaemic CRVO during 1980–7. Those without a proved diagnosis and those which had another vasoproliferative retinopathy were excluded from the study.

Twenty-seven eyes (11 right and 16 left) in 26 patients (12 males and 14 females) were included in our study. The mean period of follow-up was 30 months (range 3–93 months), and the average age of the patients was 72 years (range 47–84).

Twenty-two eyes had no other ocular disease. Of the remainder two had disciform macular degeneration, one ocular hypertension, one narrow drainage angles (treated with YAG iridotomies), and one Sjøgren's syndrome and early senile macular degeneration.

In all but five eyes prior to PRP the fundus lesions had been recorded by fundus photography and fluorescein angiography. In these five cases there was vitreous haemorrhage obscuring fundal details. Iris neovascularisation had been detected by observation of the iris and gonioscopy. The fluorescein angiograms were taken of the optic disc, posterior pole, and equatorial surveys. It was noted whether or not there was posterior segment neovascularisation, and the number of quadrants of retinal ischaemia were assessed from the amount of capillary non-perfusion.

Where no clinical review had been performed within the last three months the patients were recalled and repeat examinations performed, including repeat fundus photography and fluorescein angiography.

## Results

Twenty one eyes had fluorescein angiography prior to PRP; 17 eyes had four quadrants of capillary closure and four eyes three or fewer. In the former group eight had rubeosis and four posterior segment new vessels, and in the latter group all eyes had rubeosis iridis with a mean interval between presumed onset and PRP of four months (range three-six months). Six did not have a fluorescein angiogram before photocoagulation, as it was thought to be unnecessary for treatment: five already had rubeosis iridis and one a vitreous haemorrhage.

The pattern of neovascularisation prior to PRP and on final review in each individual patient is shown in Table 1 together with the period from probable onset of CRVO to PRP. The presenting and final patterns of neovascularisation and the regression and formation of new vessels after PRP are shown in Table 2. New vessels on the iris were present in 17 eyes at the time of PRP and new vessels on the disc or elsewhere in the retina in seven eyes. New vessels on the iris were successfully treated in 11 eyes and did not occur at any stage in nine eyes (Table 1). There were five eyes (19–23, Table 1) in which new vessels on the iris were either absent or had resolved following photocoagulation but in which posterior segment new vessels subsequently developed.

New vessels on the iris were present when the time between the probable onset (which the patient first noticed visual loss) of the CRVO and PRP was shortest (four months), new vessels on

*Table 1 The pattern of neovascularisation and time from probable onset of CRVO to PRP*

| *Number* | *Posterior new vessels* *Start* | *Posterior new vessels* *Finish* | *Anterior new vessels* *Start* | *Anterior new vessels* *Finish* | *Time from probable onset CRVO to PRP (months)* |
|---|---|---|---|---|---|
| 1 | No | No | No | No | 17 |
| 2 | No | No | No | No | 5 |
| 3 | No | No | Yes | No | 5 |
| 4 | No | No | Yes | No | 2·5 |
| 5 | No | No | Yes | No | 4 |
| 6 | No | No | Yes | No | 3 |
| 7 | No | No | Yes | No | 2 |
| 8 | No | No | Yes | No | 1 |
| 9 | No | No | Yes | No | 4 |
| 10 | No | No | Yes | Yes | 2 |
| 11 | No | No | Yes | Yes | 5 |
| 12 | No | No | Yes | Yes | 8 |
| 13 | No | No | Yes | Yes | 19 |
| 14 | NVE | No | No | No | 11 |
| 15 | NVE | No | No | No | 9 |
| 16 | VH | No | No | No | 8 |
| 17 | NVD/E | VH | No | No | 15 |
| 18 | NVD | NVD | No | No | 18 |
| 19 | No | NVE | No | No | 12 |
| 20 | No | NVD | No | No | 1 |
| 21 | No | VH | Yes | No | 5 |
| 22 | No | NVE | Yes | No | 1 |
| 23 | No | NVD/E | Yes | No | 2 |
| 24 | NVD/E | NVE | Yes | No | 3·5 |
| 25 | No | NVD | Yes | Yes | 3 |
| 26 | No | VH | Yes | Yes | 2 |
| 27 | No | VH | No | Yes | 2·5 |

NVD=new vessels on disc, NVE=elsewhere on retina, VH=vitreous haemorrhage.

*Table 2 Patterns of neovascularisation prior to, and net regression and formation of new vessels after PRP (number of eyes)*

| *New vessels* | *Pre-PRP* | *Post-PRP* | *Vessels regressed* | *Vessels formed* |
|---|---|---|---|---|
| NVD | 3 | 4 (+1 VH) | 1 | 3 |
| NVE | 4 | 4 (+1 VH) | 2 | 3 |
| NVI | 17 | 7 | 11 | 1 |
| VH | 1 | 4 | 1 | 3 (+1 NVD/E) |
| None | 5 | 12 | – | – |

NVD=new vessels on disc, NVE=elsewhere on retina, NVI=on iris, VH=vitreous haemorrhage.

*Table 3 The pattern of new vessels at PRP and the time from probable onset of CRVO to PRP*

| *Pattern of new vessels at PRP* | *Average time from probable onset of CRVO to PRP* |
|---|---|
| No NVI or NVD/E | 7·6 months (5 eyes) |
| NVD or NVE | 12 months (5 eyes) |
| NVI | 4·3 months (16 eyes) |
| NVI and NVD/E | 4 months (1 eye) |

NVD=new vessels on disc, NVE=elsewhere on retina, NVI=on iris.

the disc or elsewhere occurred when the time interval was the longest (12 months, Table 3).

Comparison of the laser therapy given to individual eyes for CRVO showed no significant difference between the number of burns administered to those with new vessels at the posterior pole after therapy (mean 2321 burns, standard deviation (SD)=1502) and those with no new vessels at the posterior pole after therapy (mean 1876 burns, SD=700). The number of laser sessions, power ranges used, spot sizes, and exposure times were similar in both groups.

Two eyes had supplementary therapy: number 4 had xenon arc photocoagulation (no neovascularisation on final review), and number 19 had cryotherapy (new vessels on the disc with vitreous haemorrhage and traction retinal detachment on final examination).

## Discussion

The pattern of neovascular response prior to PRP is similar in our series to that previously reported[4,6,7]: a preponderance for involvement of the left eye is well recorded.[3,8] None of our patients had concurrent primary glaucoma, and only one had ocular hypertension.

Our study has shown that the pattern of neovascularisation at the time of PRP can be related to the time from probable onset of CRVO to PRP (Table 3). Where rubeosis iridis occurred alone the average time from probable onset of CRVO to PRP was 4·3 months, the '100-day glaucoma', and this occurred in 16 eyes (59%). Where only posterior segment neovascularisation was present, the average time from CRVO onset to PRP was much longer (12 months). This was seen in only five eyes (19%). Those eyes with no neovascular response at the time of laser therapy showed an intermediate time (7·6 months) between probable onset of CRVO and PRP. This may suggest either that the stimulus to anterior segment neovascularisation, when present, is more intense than the stimulus to posterior segment neovascularisation or that the neovascular response of the anterior segment, once it is supplied with a hypoxic stimulus, is more rapid than that from the posterior segment. Finally it has been suggested that new vessels on the disc or elsewhere may indicate restoration of the retinal circulation[9] with a concomitant reduction in the production of an 'angiogenic factor.' This may then be insufficient to stimulate new vessels on the iris. Overall PRP was effective in inducing regression of or prophylaxis against new vessels on the iris (Table 2) but not so effective for posterior segment new vessels.

The most interesting feature of our study is the five eyes in which rubeosis either had been absent or had resolved following photocoagulation but in which posterior segment new vessels subsequently developed, whether on the disc, or elsewhere in the retina, or as shown by the presence of vitreous haemorrhage. As the posterior segment neovascularisation occurred some time after PRP, it is unlikely that a post-PRP inflammatory response was responsible for the appearance of new vessels on the disc or retina.

There is growing evidence that the neovascular response occurs due to an alteration induced by retinal hypoxia in the balance among proliferative and inhibitory growth factors produced by the retina and associated structures.[2,10,11] The original rationale for PRP was to reduce the amount of hypoxic retina and therefore reduce neovascularisation. More recent evidence suggests that photocoagulation alters the balance of the growth factors in favour of new vessel regression.

We propose a concept that, if an ischaemic CRVO occurs, the neovascular response of the affected eye varies according to the amount of hypoxic retina (Table 4), which can in turn be altered by PRP.

If hypoxia is severe, the eye responds by developing marked rubeosis iridis within three months – 100-day glaucoma. If the hypoxia is moderate then new vessels may develop on either the iris or at the posterior pole, but these occur

*Table 4 Degree of retinal ischaemia and the neovascular response*

| *Retinal ischaemia* | *Neovascular response* | *Time (months)* |
|---|---|---|
| Severe (>3 quadrants | Rubeotic glaucoma | <3 |
| Moderate (2–3 quadrants) | NVD/E +/− NVI | =6 |
| Mild (<1 quadrant) NVD/E | NVD/E | >12 |

Abbreviations as in Table 3.

later, at approximately six months after the vein occlusion. Finally, if the hypoxia, though present, is mild, then new vessels on the iris are very rare; new vessels, however, may develop at the posterior pole many months after the central retinal vein occlusion. Thus a severely ischaemic eye may be converted to a mildly ischaemic eye by PRP. This correlates with those eyes in this study with new vessels on the iris which subsequently developed new vessels elsewhere even after an 'adequate' PRP and resolution of the anterior segment neovascularisation. Therefore it is important that these patients should still remain under regular review.

The visual outcome following CRVO is generally poor, so that the usual aim of PRP is to convert a painful blind eye into a comfortable eye, but with poor visual potential. It has been said[9] that if new vessels on the disc or retina occur the eye is saved, but if they occur on the iris then the eye is lost. Therefore converting an eye with new vessels on the iris to one with them on the disc or elsewhere on the retina may be an acceptable goal for PRP.

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# Retinal circulation times in diabetes mellitus type 1

Bernd Bertram, Sebastian Wolf, Susanne Fiehöfer, Karin Schulte, Oliver Arend, Martin Reim

## Abstract

**Video fluorescein angiography was performed in 124 patients between 18 and 65 years of age (mean 35·0, SD 12·3 years) with juvenile-onset, insulin-dependent diabetes mellitus (type 1). The arm-retina time (ART) and the retinal arteriovenous passage time (AVP) were measured by means of a picture analysis system to quantify the retinal microcirculation. Glucose metabolism was assessed by the blood level of haemoglobin A1c. The ART 11·5, SD 3·4 s) was similar to that in normal persons (11·2, SD 3·3 s), while the AVP was significantly longer in the diabetics (AVP=2·35, SD 0·87 s) than in normal persons (AVP=1·45, SD 0·40 s). The patients with severe diabetic retinopathy showed the most impressive change in AVP. The diabetics with good glycaemic control, that is, with glycosylated haemoglobin (HbA1c) ≤8·0 g/dl, had a shorter AVP than patients with bad glycaemic control (HbA1c ≥9·5 g/dl). The group with a history of diabetes for less than five years showed circulation parameters similar to those of normal persons. The AVP in this group was significantly shorter than in groups with a history of diabetes for five or more years.**

Most patients with diabetes mellitus develop characteristic abnormalities of the retinal blood vessels and the blood rheology. These abnormalities seem to alter the retinal blood flow in diabetic persons.

Video fluorescein angiography, combined with a picture analysing system, is a clinically applicable objective method for evaluating retinal circulation parameters.[1] Until August 1989 the system included a low light videocamera (Bosch) and a fundus camera (C Zeiss). Thereafter both devices were replaced by a scanning-laser-ophthalmoscope (SLO, Rodenstock). This new SLO gave similar results.[2] The measuring technique used has been presented in detail elsewhere.[1] The present paper reports the measurement of retinal circulation in juvenile-onset insulin dependent diabetic persons (type 1) by means of video fluorescein angiography.

## Materials and methods

We studied 124 patients with juvenile-onset insulin dependent diabetes mellitus (type 1) (71 male, 53 female) aged between 18 and 65 years (mean 35·0 SD, 12·3 years). The history of diagnosed diabetes ranged between 0·1 and 51·4 years (mean 18·5, SD 10·3 years). Twenty one patients (16·9%) had a history of systemic hypertension. No other retinal or systemic disease was found in any patient. The results obtained from diabetics were compared with those of an age-matched control group of apparently healthy volunteers. The characteristics of the diabetic and the normal subjects are summarised in Table 1. No significant difference between the groups was found with respect to age and systolic and diastolic blood pressure.

*Table 1 Characteristics of juvenile-onset diabetics and normal subjects*

| | *Diabetics (n=124)* | *Normal (n=75)* |
|---|---|---|
| Sex M/F | 71/53 | 30/45 |
| Age (yr) | 35 (12) | 32 (13) |
| Duration of diabetes (yr) | 18 (10) | – |
| HbA1c (g/dl) | 8·8 (1·9) | – |
| Systolic blood pressure (mmHg) | 135 (25) | 134 (13) |
| Diastolic blood pressure (mmHg) | 81 (12) | 77 (9) |
| History of hypertension (%) | 16·9 | – |

SD in parentheses

The severity of diabetic retinopathy was evaluated by ophthalmoscopy, fundus photography, and angiography. The diabetic patients were distributed into four groups: (1) no retinopathy (DR 0); (2) mild to moderate non-proliferative retinopathy (that is, microaneurysms, haemorrhages, hard exudates) (DR 1); (3) preproliferative retinopathy (that is, multiple cotton-wool spots, intraretinal microvascular abnormalities, venous beading, or areas of non-perfusion) (DR 2); (4) proliferative retinopathy (DR 3).

Glucose metabolism was assessed by the blood level of glycosylated haemoglobin (HbA1c) (normal range: 4·3–6·0 g/dl).[3]

We found a significant difference in age and duration of diabetes (*a*) between diabetics with no retinopathy (DR 0) and the other groups (p<0·01) and (*b*) between diabetics with mild to moderate non-proliferative retinopathy (DR 1) and proliferative retinopathy (DR 3) (p<0·05). There was no significant difference between the groups regarding sex and glycaemic control (HbA1c). A significantly increased systolic and diastolic blood pressure was found in patients with proliferative retinopathy (DR 3) as compared with the other groups.

Video fluorescein angiography was performed on all subjects. The circulation parameters arm-retina time (ART) and retinal arteriovenous passage time (AVP) were measured by means of a picture analysing system.[1] The ART consists of the period of time between the injection of dye into the cubital vein and its first appearance in

*Table 2 Circulation parameters of juvenile-onset diabetic and normal subjects*

| | *No* | *Arm-retina time (s)* | *Arteriovenous passage time (s)* |
|---|---|---|---|
| Diabetic patients | 124 | 11·5 (3·4) | 2·35 (0·87) |
| Normal subjects | 75 | 11·2 (3·3) | 1·45 (0·40) |
| Significance | | NS | p<0·01 |

SD in parentheses.

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the retinal arteries. It allows a rough estimation of the macrocirculation. The AVP is defined as the interval between the first influx of dye into a retinal artery and its first appearance in the corresponding retinal vein. It is the time the indicator requires for passing through a corresponding area of retinal microcirculation.

### STATISTICS

Mean value and standard deviation are given for all samples. To assess the significance of the results non-parametric tests (Mann-Whitney U test; Kruskal-Wallis test) were used. For multiple group test statistics the Kruskal-Wallis test with subsequent Holm's sequential rejective multiple test procedure[4] was applied. Findings with an error probability value smaller than 0·05 were considered to be statistically significant.

## Results

Table 2 shows the circulation parameters of juvenile-onset diabetic and normal subjects. The arm-retina time was similar in both groups. A significant prolongation of the AVP in diabetics was found.

The influence of the stage of diabetic retinopathy on the circulation parameters is shown in Table 3. No significant difference of arm-retina time was found between the groups. The AVP was significantly prolonged in all four groups as compared with the normal subjects. There was an increase of AVP with progressing diabetic retinopathy. The differences in AVP between RD 0 and RD 1 (p<0·05), RD 0 and RD 2 (p<0·05), RD 0 and RD 3 (p<0·01), and RD 1 and RD 3 (p<0·01) were significant. HbA1c was unchanged throughout the various stages of diabetic retinopathy.

To determine the influence of glycaemic control on the circulation parameters groups with good (HbA1c ≤8·0 g/dl) and bad glycemic control (HbA1c ≥9·5 g/dl) were compiled. Patients with an HbA1c concentration between 8·1 and 9·4 g/dl were not included. There was no significant difference in the arm-retina time between the two groups. The diabetics with bad glycaemic control showed a significant increase of AVP as compared with patients with good glycaemic control (Table 4).

Table 5 shows the AVP of juvenile-onset diabetics with good and bad glycaemic control and stage of diabetic retinopathy. Diabetics without any sign of retinopathy (DR 0) and with good glycaemic control showed an AVP similar to that of healthy individuals. In mild to moderate non-proliferative retinopathy (DR 1) and in preproliferative retinopathy (DR 2) the AVP was significantly (p<0·01) longer in patients with bad glycaemic control than in diabetics with good glycaemic control. The AVP of diabetics with proliferative retinopathy (DR 3) seemed to be independent of glycaemic control.

*Table 3* *Circulation parameters of juvenile-onset diabetics and stage of diabetic retinopathy (DR) (DR0 no retinopathy; DR1: mild to moderate non-proliferative retinopathy; DR2· preproliferative retinopathy; DR3: proliferative retinopathy)*

| *Stage of DR* | *No* | *Arm-retina time (s)* | *Arteriovenous passage time (s)* |
|---|---|---|---|
| DR 0 | 27 | 11 5 (3·5) | 1·84 (0 67) |
| DR 1 | 39 | 11 1 (2 8) | 2·28 (0 78) |
| DR 2 | 22 | 11 1 (3·1) | 2 44 (0·88) |
| DR 3 | 36 | 12·2 (4 2) | 2 75 (0·91) |
| Significance | | NS | p<0 01 |

SD in parentheses

*Table 4* *Arm-retina time (ART) and arteriovenous passage time (AVP) of juvenile-onset diabetics with good (HbA1c ≤8 0 g/dl) and bad glycaemic control (HbA1c ≥9 5 g/dl)*

| | *No.* | *ART (s)* | *AVP (s)* | *HbA1c (g/dl)* |
|---|---|---|---|---|
| Good glycaemic control | 35 | 11·4 (3·2) | 1 90 (0·67) | 7·0 (0 8) |
| Bad glycaemic control | 34 | 11·1 (2·9) | 2 62 (0 86) | 10·8 (1 3) |
| Significance | | NS | p<0·01 | p<0 01 |

SD in parentheses

*Table 5* *Arteriovenous passage time (AVP) of juvenile-onset diabetics with good (HbA1c ≤8·0 g/dl) and bad glycaemic control (HbA1c ≥9·5 g/dl) and stage of diabetic retinopathy (DR) (DR0: no retinopathy; DR1: mild to moderate non-proliferative retinopathy; DR2: preproliferative retinopathy, DR3: proliferative retinopathy) (*=p <0·01 between good and bad control)*

| *Stage of DR* | *Good glycaemic control AVP (s)* | *Bad glycaemic control AVP (s)* |
|---|---|---|
| DR 0 | 1·40 (0 59):n=8 | 1 98 (0·51) n=5 |
| DR 1 | 1·86 (0 40) n=12 | 2 51 (0 36*):n=10 |
| DR 2 | 1·84 (0 44) n=9 | 3 00 (1·03*):n=8 |
| DR 3 | 2·71 (0 85) n=6 | 2 82 (1·05):n=11 |

SD in parentheses

*Table 6* *Circulation parameters of juvenile-onset diabetics and duration of diagnosed diabetes*

| *Duration of diabetes (yr)* | *No* | *Arm-retina time (s)* | *Arteriovenous passage time (s)* |
|---|---|---|---|
| <5 | 9 | 11 4 (2·1) | 1 56 (0 48) |
| 5–14 | 40 | 11·1 (3·6) | 2 24 (0·87) |
| 15–24 | 48 | 11·0 (2·9) | 2 52 (0·94) |
| ≥25 | 27 | 13 0 (4·1) | 2·47 (0·69) |

SD in parentheses

The influence of the duration of diabetes on the circulation parameters is shown in Table 6. The group with a history of diabetes <5 years had a normal ART and AVP as compared with healthy persons. Six of nine diabetics with duration of diabetes <5 years had a value of HbA1c ≤7·5 g/dl. The AVP in this group is significantly shorter than in the other three groups with duration of diabetes ≥5 years (p<0·01). No significant change of AVP was found among the other groups (duration of diabetes: 5–14, 15–24, and ≥25 years). The ART of the three groups <25 years was similar to the ART of healthy persons. Only the group with duration of diabetes ≥25 years showed an increased arm-retina time (p<0·05) as compared with healthy persons and with diabetics with a history of diabetes for 5–14 and 15–24 years.

## Discussion

The initial lesions of diabetic retinopathy affect capillaries, small arterioles, and venules. The earliest changes are retinal capillary bed obstructions and capillary dropout.[5] Progressive thickening of the basement membrane narrows the lumen of capillaries; microaneurysms, venous abnormalities, arteriovenous shunts, and later neovascularisation develop. These changes of vessel morphology may disturb the retinal microcirculation.

Furthermore, diabetes mellitus affects the blood rheology. Increasing blood viscosity and plasma viscosity,[6-8] increasing red blood cell aggregation,[8-10] and increasing platelet aggregation and change of platelet shape[11,12] reduce the retinal blood flow, if not compensated by regulatory means.

The AVP is the shortest time of fluorescein circulating through a corresponding area of retinal microcirculation. We found an increased AVP in adult type 1 diabetics. This indicates a disturbed microcirculation. Previous work had suggested that retinal blood flow would be increased in prediabetes[13] and in some stages of diabetic retinopathy.[14-16] However, our finding of increased AVP is in agreement with other investigations of decreased retinal blood flow or increased retinal circulation times using the blue light entoptic phenomenon,[17,18] laser Doppler velocimetry,[19] photoangiography,[20,21] or two-point fluorophotometry.[22] With video fluorescein angiography we found prolonged AVP in type 2 diabetics.[23,24] These methods of measuring retinal circulation evaluate different parts of the retinal circulation. The blue light entoptic phenomenon[17,25] allows determination of the perifoveal flow velocity of leucocytes; laser Doppler velocimetry measures the velocity of red blood cells.[19] Two-point fluorophotometry[15,16] measures blood flow velocities in the major retinal vessels; two-point fluorophotometry,[22] photoangiography,[20,21] and with more precision video fluorescein angiography measure the time interval of fluorescein from arteriole to the corresponding venule. In capillaries of the conjunctiva bulbi[26,27] and of the nailfold[28] a decreased blood velocity was also found in diabetics. The prolonged AVP may be due to the morphological changes of the retinal vessels and to the disturbed blood rheology in diabetes mellitus.

By means of photoangiography Ferrer[20] found retinal circulation times of four long-standing diabetics without retinopathy to be similar to that of normal persons. Two cases of long-standing diabets with retinopathy were found to have a delayed circulation. Kohner *et al.*[14] showed that the mean transit time is decreased in no or mild diabetic retinopathy and bears normal values in moderate and in severe retinopathy. Cunha-Vaz *et al.*[15] found an increase of retinal blood flow in minimal and more advanced stages of background retinopathy and decreasing retinal blood flow in proliferative retinopathy. Blair *et al*[29] found that mean circulation time is normal in no or background retinopathy and prolonged in proliferative retinopathy. Yoshida *et al*[22] reported that mean circulation time was significantly increased only in proliferative retinopathy and similar to that of normal persons in no or non-proliferative retinopathy. In a study of Grunwald *et al*[19] arterial and venous blood flow was less than normal in background and proliferative retinopathy and similar to that of normal persons in diabetics with no retinopathy. The calculated volumetric blood flow rate, however, did not differ from normal in all stages of retinopathy without retinal photocoagulation.[19] Rimmer *et al*[18] reported in a long-term follow-up study that the perifoveolar blood velocity (measured by blue light entoptic phenomenon) decreased in the course of diabetic retinopathy.

In our investigation a larger number of a specific subgroup of diabetics (adult juvenile-onset insulin dependent) was studied than reported elsewhere. All groups of different stages of diabetic retinopathy showed a prolonged AVP. There was a trend to increasing AVP with progressing diabetic retinopathy.

Dependence of the retinal blood flow on the duration of diabetes mellitus was examined by Oswald *et al.*[16] They reported an increase of blood flow velocity, with a maximum among patients with a 10–20 years' history of diabetes mellitus. In contrast, we found a normal AVP in patients with a history of diabetes of less than five years and a worse retinal microcirculation in diabetics with longer duration of the disease.

By means of blue field entopic phenomenon Fallon *et al.*[30] and Davies *et al*[25] showed that acute fluctuations in plasma glucose levels are not associated with changes of perifoveal blood flow. In addition, no difference was found in the response of macular blood flow to hyperoxia (autoregulation) with high and normal blood glucose levels.[30] Laser Doppler velocimetry[19] did not show any correlation between acute blood glucose levels and arterial or venous blood flow velocity in insulin dependent diabetics. In 12 type 2 diabetics Grunwald *et al*[31] found a decreasing retinal blood flow within three hours after onset of a decrease in blood glucose from hyperglycaemia to normoglycaemia. The study presented here showed AVP of diabetics with good or bad long term diabetic control within the last 4–6 weeks before examination (HbA1c). The diabetics with bad glycaemic control showed a longer AVP than did patients with good glycaemic control. Diabetics without signs of retinopathy (DR 0) and good glycaemic control had a similar AVP as compared with healthy persons. These results may indicate that bad glycaemic control worsens the retinal microcirculation and may lead to a more severe course of diabetic retinopathy. In the proliferative stage the retinal microcirculation was even more disturbed. Only in this group did the AVP seem to be independent of good glycaemic control.

The ART allows for a rough estimation of the macrocirculation. The type 1 diabetics studied here showed similar values of ART to those of healthy adults. Only the patients with history of diabetes ≥25 years showed an increased ART (Table 6). This may indicate that only some of the patients with a long history of diabetes participating in this study suffered from disturbed macrocirculation. Disturbed macrocirculation is an unlikely cause of increased AVP because of the normal ART we encountered in most of the diabetics.

In conclusion, the retinal circulation in juvenile-onset insulin dependent adult diabetics is decreased as compared with that of healthy persons. AVP values similar to those of normal persons were found only in diabetics (1) with duration of diabetes of less than five years or (2) without retinopathy and with good glycaemic control. Bad glycaemic control seems to worsen retinal microcirculation. This may be one cause of the increasing prevalence of ischaemic lesions and their vascular complications in patients with a long history of diabetes mellitus.

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# Pulsatile ocular blood flow in patients with low tension glaucoma

C B James, S E Smith

**Abstract**

**Measurements of the intraocular pressure (IOP) pulse and pulsatile ocular blood flow (POBF) have been made in 22 patients with bilateral low tension glaucoma (LTG) and 29 healthy subjects matched as closely as possible for age, refractive error, IOP, systemic pulse pressure, and heart rate. Recordings were made in both the standing and supine positions. The amplitude of the intraocular pressure pulse was significantly lower in patients with LTG (1·2, SEM 0·1 mmHg standing, and 1·3, SEM 0·1 mmHg lying) than in healthy subjects (1·9, SEM 0·1 mmHg standing, and 2·0 SEM 0·1 mmHg lying): p<0·001 standing and p<0·002 lying. Measurement of POBF also showed a significant reduction between the healthy subjects (428 (31) SEM µl/min standing and 345 (28) SEM µl/min lying) and subjects with LTG (301 (27) SEM µl/min standing and 249 (24) SEM µl/min lying), p<0·005 standing and p<0·02 lying. This represents a difference of approximately 30% between the two groups in either posture. A close non-parametric correlation existed between the level of IOP and the POBF (r=0·75, p<0·001 standing, and r=−0·55, p<0·02 lying). Such a correlation was not present in the healthy subjects. A reduction in POBF occurred in both groups on assuming the supine posture (healthy subjects 83 (16) SEM µl/min, LTG subjects 52 (17) SEM µl/min). These figures represent reductions of 19% and 17% respectively in comparison with the standing value. The results lend further confirmation to the hypothesis that vascular factors are associated with low tension glaucoma.**

Low tension glaucoma (LTG) can be defined as the development of typical glaucomatous optic disc cupping and field damage in patients with normal iridocorneal angles and intraocular pressure (IOP) within the statistically normal range. Some regard the condition as separate from chronic open angle glaucoma (COAG), whereas others regard it as representing one end of the glaucoma spectrum.[1] Much interest has centred on the vascular origins of LTG. In an extensive review Levene examined the role of systemic hypertension, generalised vascular disease, reduced ophthalmic artery pressure, and retinal vascular occlusion.[2] He concluded that the evidence of an association with any of these factors is at best uncertain. Subsequent work has confirmed this view.[3]

Better evidence exists for small vessel occlusion producing a sector infarct of the optic nerve linked to the presence of a splinter haemorrhage.[2,4] An increased incidence of migraine,[5,6] a reduced response of peripheral blood flow to cold,[7] and a reduced compliance of the optic nerve head to a raised IOP measured by the visual evoked response[8] have also been reported. Schulzer *et al* have recently suggested that in both LTG and COAG there may be two groups of patients – one with predominantly IOP related disease and one with vascular disease.[9] These observations lend further corroboration to the theory that reduced perfusion, however caused, is at least a factor in the pathogenesis of LTG.

Clinically assessment of blood flow in the eye and optic disc has depended on the analysis of fluorescein angiograms. In both COAG and LTG hypofluorescence of the disc and prolonged fluorescein transit times have been reported.[10-12] Hypofluorescence is more likely to be focal in LTG.[10] A prolongation in transit time and choroidal filling have also been reported in patients with progressive LTG in comparison with those in whom the visual field defect did not appear to progress.[13]

An additional method for the examination of ocular pulsatile bloodflow is available. The ocular pressure pulse originates from blood filling the choroidal vasculature during cardiac systole.[14] The intraocular pressure pulse has been observed to be reduced in patients with LTG.[15] A method of analysis of the ocular pulse has been devised which converts the pressure pulse into a volume pulse, and with knowledge of the heart rate a measure of the pulsatile ocular bloodflow (POBF) can be calculated.[16,17] As the choroidal and anterior optic disc circulations share a common source from the posterior ciliary arteries a reduction in choroidal circulation may well reflect a reduction in optic nerve head perfusion. Altered choroidal circulation is not, however, the only factor that will affect the intraocular pressure pulse. Additional factors include the initial level of IOP,[18] the systemic pulse pressure,[19] and, as shown by recent work in this department, the ocular volume and the heart rate. The aim of this study was to measure the ocular pulse and the derived POBF in patients with LTG and compare the results with those obtained in a group of healthy volunteers matched as closely as possible for the factors outlined above.

## Material and methods

### PATIENTS AND VOLUNTEERS

Twenty-two patients, 12 male and 10 female, with bilateral LTG were examined in this study. Low tension glaucoma was diagnosed if the patient had typical glaucomatous cupping, glaucomatous field defects, normal iridocorneal angles on gonioscopy, and no IOP off treatment

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greater than 22 mmHg during either day or 24-hour phasing. No patient had any neurological deficit. One patient with a cataract extraction but no patients with trabeculectomy were included in this study. One patient was observed to have slight senile macular changes on fundal examination. Ten patients taking topical ocular hypotensive medication stopped this for two weeks prior to measurement. Two patients were taking systemic B adrenoceptor blocking drugs, one was taking systemic B adrenoceptor blocking drugs and isosorbide dinitrate, three were taking nifedipine, two were on thiazide diuretics, and two were on digoxin.

Twenty-nine healthy volunteers, six male and 23 female, on no medication and with no significant past ocular history, matched as closely as possible for age, refractive error, IOP, systemic pulse pressure, and heart rate, were measured as a control group. Table 1 outlines these variables for the two groups. Written consent was obtained from each subject after full explanation of the procedure had been given. Measurements were performed randomly in both groups between the hours of 0900 and 1800.

### MEASUREMENTS

Intraocular pressure and the ocular pulse were measured in both eyes with a pneumotonometer linked to a Langham Ocular Blood Flow System after instillation of local anaesthetic (benoxinate). Heart rate was determined simultaneously with an electrocardiograph (ECG). The POBF was calculated as previously described.[20, 21]

The blood pressure was recorded with an autosphygmomanometer (Takeda Medical) and an arm cuff level with the heart in both upright and supine postures. The mean blood pressure was calculated as diastolic pressure +⅓ of the pulse pressure.

The following protocol was observed for both groups of subjects. Refractive and slit-lamp examination and funduscopy were first performed on all subjects. Prior to measurement the subject rested seated for 10 minutes. This was followed by a period of 5 minutes standing. Measurement of blood pressure and pneumotonometric recordings were then made. The subject then lay down for 15 minutes using one pillow as a headrest, and the procedure was repeated. The pneumotonometer calibration was checked immediately before each patient was measured and at each change in posture.

*Table 1 Characteristics of the two study groups*

| | *Healthy subjects* | | *Low tension glaucoma* | | |
|---|---|---|---|---|---|
| | *Mean (SEM)* | *Range* | *Mean (SEM)* | *Range* | *p* |
| Age (yr) | 51 (1·8) | 29/73 | 70·3 (2·3) | 48/87 | 0·0001 |
| Refraction (dioptres) | 0 (0·3) | −5·5/2·7 | −0·3 (0·6) | −7·75/4 | NS |
| Standing IOP (mmHg) | 17·4 (0·3) | 11·4/23·2 | 17·8 (0·5) | 12·4/21·1 | NS |
| Lying IOP (mmHg) | 19·6 (0·6) | 13·9/26·8 | 20·5 (0·5) | 15·6/25·4 | NS |
| Standing MBP (mmHg) | 99 (2) | 81/126 | 105 (3) | 82/129 | NS |
| Lying MBP (mmHg) | 90 (2) | 75/125 | 99 (3) | 80/130 | 0·02 |
| Standing SPP (mmHg) | 46 (3) | 24/119 | 54 (4) | 23/81 | NS |
| Lying SPP (mmHg) | 47 (2) | 24/94 | 52 (3) | 31/78 | NS |
| Standing HR (bpm) | 70 (1) | 58/86 | 79 (4) | 49/114 | 0·02 |
| Lying HR (bpm) | 59 (1) | 48/74 | 66 (3) | 48/93 | 0·03 |

MBP=mean blood pressure. SPP=systemic pulse pressure. HR=heart rate.

*Table 2 Mean (SEM) for the ocular variables measured in upright and supine postures*

| | *Healthy subjects* | | *LTG subjects* | |
|---|---|---|---|---|
| | *Standing* | *Lying* | *Standing* | *Lying* |
| Pulse amplitude mmHg | 1·9 (0·1) | 2·0 (0·1) | 1·2 (0·1) | 1·3 (0·1) |
| Pulse volume (μl) | 6·0 (0·5) | 5·7 (0·4) | 3·9 (0·3) | 3·8 (0·34) |
| POBF μl/min | 428 (31) | 345 (28) | 301 (27) | 249 (24) |

### STATISTICAL ANALYSIS

Differences between subjects were assessed with unpaired *t* tests. Within-subject differences were analysed with paired *t* tests. Spearman's non-parametric regression analysis was used to determine the relationship between IOP and POBF in both groups.

## Results

### DIFFERENCES BETWEEN GROUPS

No significant difference was found between the right and left eyes in either of the two groups; thus only the results for the right eyes will be quoted. The results of the ocular pulse and POBF measurements are shown in Table 2. There was a significant difference in the amplitude of the ocular pulse between the two groups of 0·7 mmHg standing and lying ($p<0\cdot001$ standing, $p<0\cdot002$ lying) (Fig 1). Similarly the ocular pulse volume was significantly less in the LTG group by 2·1 μl standing and 1·9 μl lying ($p<0\cdot001$ standing and $p<0\cdot01$ lying). The POBF was also significantly reduced in the patients with LTG, 127 μl/min standing and 96 μl/min lying ($p<0\cdot01$ and $p<0\cdot02$ respectively) (Fig 2). This represents a lower POBF in patients with LTG than was seen in healthy subjects of approximately 30% in either posture.

A significant non-parametric relationship existed between IOP and POBF in the subjects with LTG ($R=-0\cdot75$, $p<0\cdot001$ standing, $R=0\cdot55$, $p<0\cdot02$ lying) (Fig 3). No such relationship was seen in the healthy subjects ($R=0\cdot16$, NS standing, $R=0\cdot06$, NS lying) (Fig 4).

### POSTURAL DIFFERENCES

There was a significant increase in IOP on assumption of the supine position (2·7 (SEM 0·3) mmHg, $p<0\cdot001$ in the LTG subjects, and 2·2 (SEM 0·4) mmHg, $p<0\cdot001$ in the healthy subjects), but the difference between the two

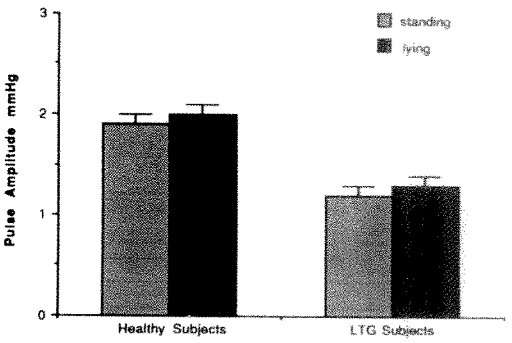

*Figure 1 Pulse amplitude in healthy subjects and those with LTG showing the effect of postural change.*

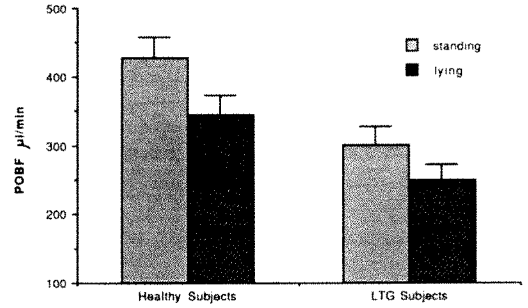

*Figure 2 POBF in healthy subjects and those with LTG showing the effect of postural change.*

groups was not significant. The pulse amplitude in the LTG subjects increased slightly on lying (0·1 (SEM 0·1) mmHg, $p<0{\cdot}05$), but no other significant postural changes in the characteristics or derivatives of the ocular pulse was seen in either of the groups (Table 2). A reduction in POBF was seen on lying down in both healthy subjects (83 (SEM 16) µl/min $p<0{\cdot}001$) and in the LTG subjects (52 (SEM 17) µl/min, $p<0{\cdot}006$) (Fig 2). This represented a reduction in flow of 19% and 17% ($p<0{\cdot}001$ and $p<0{\cdot}006$) respectively.

Postural changes occurred in both groups in mean blood pressure (9 (SEM 1) mmHg healthy subjects $p<0{\cdot}001$, 6 (SEM 2) mmHg in the LTG group $p<0{\cdot}002$) and heart rate (11 (SEM 1) bpm, $p<0{\cdot}001$ in healthy subjects, 13 (SEM 2) bpm, $p<0{\cdot}001$ in the LTG group). There was no significant postural change in the systemic pulse pressure.

## Discussion

Our results show that there is an overall reduction in ocular pulse amplitude, pulse volume, and POBF in subjects with LTG in comparison with a normal volunteer control group. Previous measurements of the ocular pulse amplitude in LTG have been inconclusive. Perkins reported a reduction in the ocular pulse amplitude.[15] Lambrou *et al* found no difference in the pulse amplitude but did find a reduction in pulse volume measurements in subjects with LTG.[22] Comparison of ocular pulse measurements between groups is complicated by the numerous factors which may alter ocular pulse amplitude other than the pulsatile flow of blood into the choroidal vasculature. Initial IOP, ocular volume, and heart rate will all affect the size of the ocular pressure pulse. A correlation between systemic pulse pressure and ocular pulse amplitude has also been reported.[19] We have attempted to match these variables in the two study groups. Intraocular pressure in the two groups was similar. Refractive error was also similar. Refractive error if axial will be proportional to the length of the eye and hence if the eye is assumed to be spherical will be proportional to ocular volume. Tomlinson and Leighton[23] found no significant difference in axial length between normal subjects and LTG patients with equivalent refractions. Matching for refractive error should ensure matching for ocular volume.

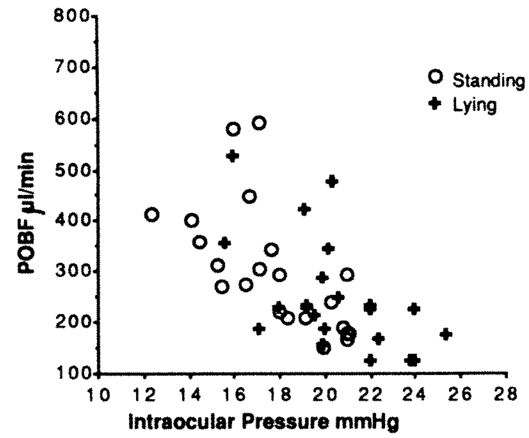

*Figure 3 The relation between IOP and POBF in LTG subjects.*

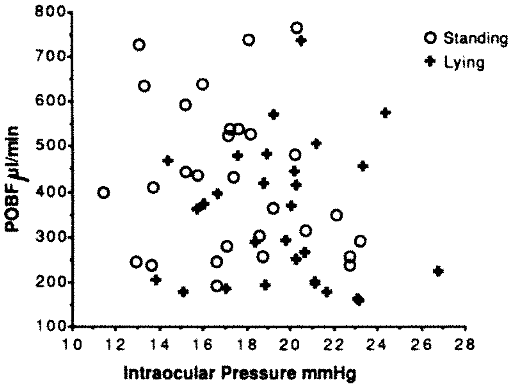

*Figure 4 The relation between IOP and POBF in healthy subjects.*

In our study the LTG subjects differed from their controls in two respects. First, they were older by 19 years. No significant changes in choroidal blood flow with age, by indocyanine green dye methods to measure blood flow, have been demonstrated unless macular degenerative changes are present.[24] Only one LTG subject in this study had slight macular changes. An alteration in scleral rigidity will affect the size of the ocular pulse and calculations made from it. Slight changes do occur with age, though there is considerable variation.[25] It is not likely that a change in scleral rigidity over the age difference seen here would be significant. Secondly, the LTG subjects had a slightly faster pulse rate (Table 1). This would tend to increase rather than reduce POBF but may reduce the amplitude of the pulse pressure. For the difference in heart rate observed the difference would be only small. It thus appears reasonable to assume that the observed differences between groups are not artifactually caused by differences in systemic or ocular factors not directly related to pulsatile ocular blood flow but reflect a real reduction in both the ocular pulse amplitude and POBF in patients with LTG. These results compare with measurements made in patients with COAG, where a reduction of POBF was found, though to a lesser degree, than were found in the LTG patients in this study.[21]

The importance of vascular factors in the aetiology of both LTG and COAG has been debated for many years.[26–28] Pathologically there is a decrease in the vascularity of the optic disc in glaucomatous eyes.[29,30] It is impossible to know whether this is a result or cause of glaucomatous optic nerve damage, however. Much experimental work has centred on the effect of raised IOP as a means of altering the perfusion pressure of the optic nerve.[31–34] This suggests that optic nerve blood flow is not affected until the IOP is significantly raised – that is, the circulation displays autoregulation. Experiments in primates show that the chronic glaucoma model is associated with the same pattern of nerve fibre loss as is seen in human glaucoma.[35] Studies with tritiated iodoantipyrine[32] on this model have, however, failed to show a significant reduction in optic nerve blood flow. This work has been performed in previously healthy animal eyes, and care must be taken in interpreting the findings in the human glaucomatous eye, where, for example, autoregulation of optic nerve blood flow may be deficient or a reduction in optic nerve blood flow may be a second and independent factor in the aetiology of glaucomatous damage. Examination of the metabolic function of the optic nerve head[36] has shown that relatively small changes in mean arterial pressure or increases in IOP may result in metabolic dysfunction of the optic nerve head which appear to be ischaemic in origin. Chronic reduction of ocular blood flow despite an IOP within the statistically normal range may thus result in metabolic or ischaemic damage to the optic nerve head. The finding in this study of a reduced POBF in LTG is therefore of great interest, as it suggests that eyes with LTG may indeed be susceptible to chronic metabolic dysfunction.

The measurement of POBF is essentially one of choroidal rather than anterior optic nerve blood flow. Although both circulations are derived from the posterior ciliary supply,[37] caution must be used in drawing conclusions on anterior optic nerve blood flow from choroidal flow which appears not to demonstrate autoregulation.[38 39] Measurement of pulsatile blood flow will also not take account of any non-pulsatile flow that may be present. Doppler studies have revealed moving blood in the ophthalmic artery during diastole,[40] though the extent to which such non-pulsatile flow contributes to total perfusion of the optic nerve head is at present unknown.

The close relationship between IOP and POBF seen in this study is also of particular interest (Fig 3). A relationship between asymmetric glaucomatous damage with asymmetric IOP has been reported, the eye with the higher pressure suffering the most damage.[41–42] Our findings suggest that as well as a relatively elevated IOP these eyes may also suffer from a reduced pulsatile blood flow.

A postural reduction in POBF was seen in both groups of subjects. The relationship between pulsatile and non-pulsatile flow may also be affected by postural change, however. Perfusion pressure will alter on assumption of the supine posture. A rise in IOP and venous pressure and a fall in mean blood pressure (Table 1) will reduce perfusion pressure, but a larger fall in arterial hydrostatic pressure will increase perfusion pressure. An observed postural increase in ophthalmic perfusion pressure of 10 mmHg[43] fits well with these changes. An increase in the ophthalmic artery blood velocity during diastole has also been reported.[40] One might thus expect to see an increase in non-pulsatile flow in the supine position. The relationship for total blood flow is more complex, for this is also determined by pulse rate, which decreases in the supine position (Table 1). At decreased pulse rates not only would total blood flow fall but the proportion of pulsatile to non-pulsatile flow would be expected to increase. These complex relationships make it difficult to assess whether the fall in POBF reflects a postural fall in total blood flow or not. During sleep, however, when heart rate and mean arterial pressure fall further, an already reduced ocular circulation may be compromised.

## Conclusion

Using a pneumotonometer linked to a Langham Ocular Bloodflow system we have recorded the ocular pulse in a group of subjects suffering from LTG and a carefully matched control group. Using previously established techniques we have derived a measure of the POBF in both groups. A significant reduction in both the ocular pulse amplitude and the POBF has been found in patients suffering from LTG. In both groups there was a significant reduction in POBF on lying. In LTG subjects a close correlation between IOP and POBF was found. These results lend further weight to the theory that vascular factors are associated with the development of LTG and critical underperfusion is causative of damage to the optic nerve head, particularly when the subject is supine. Further research to elucidate the effect of reducing IOP on blood flow in these patients and to determine methods of improving ocular blood flow may be helpful in treating this condition.

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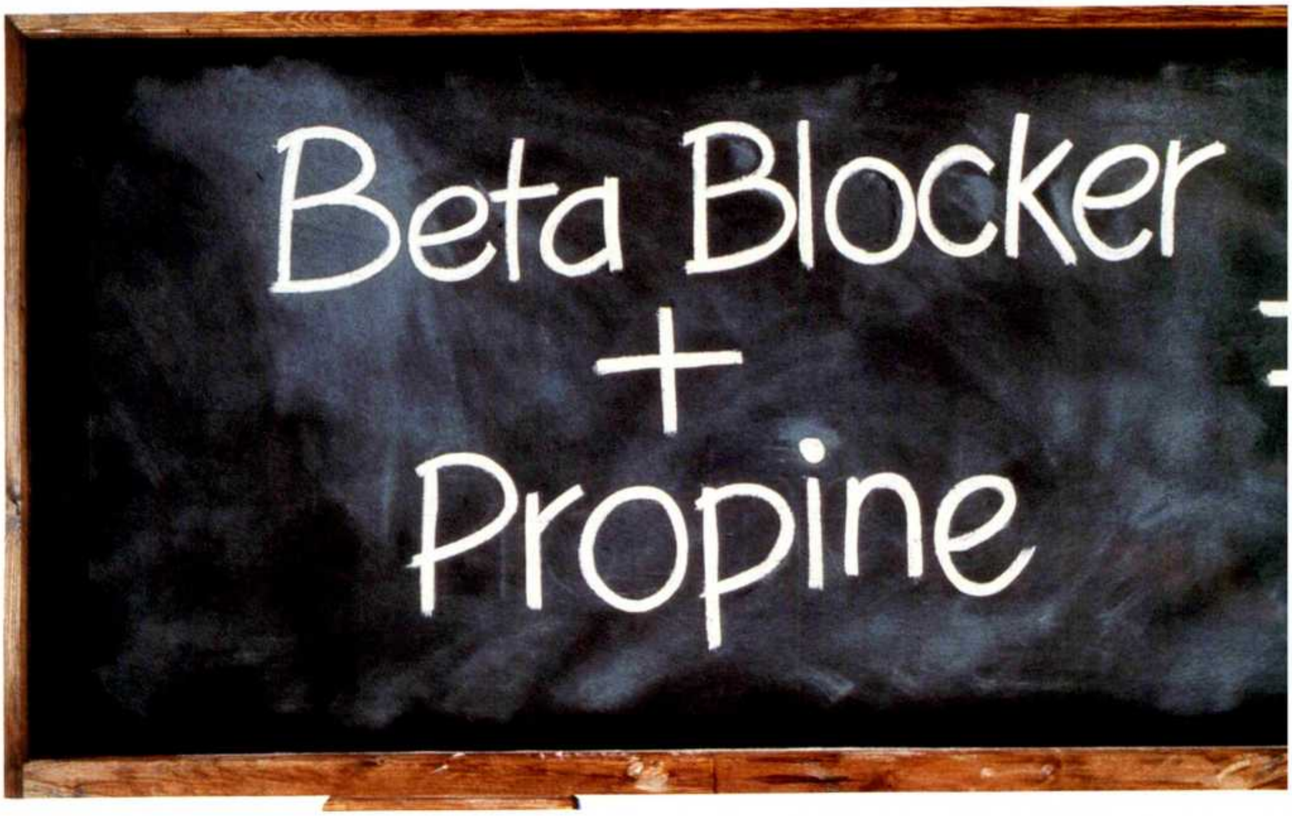

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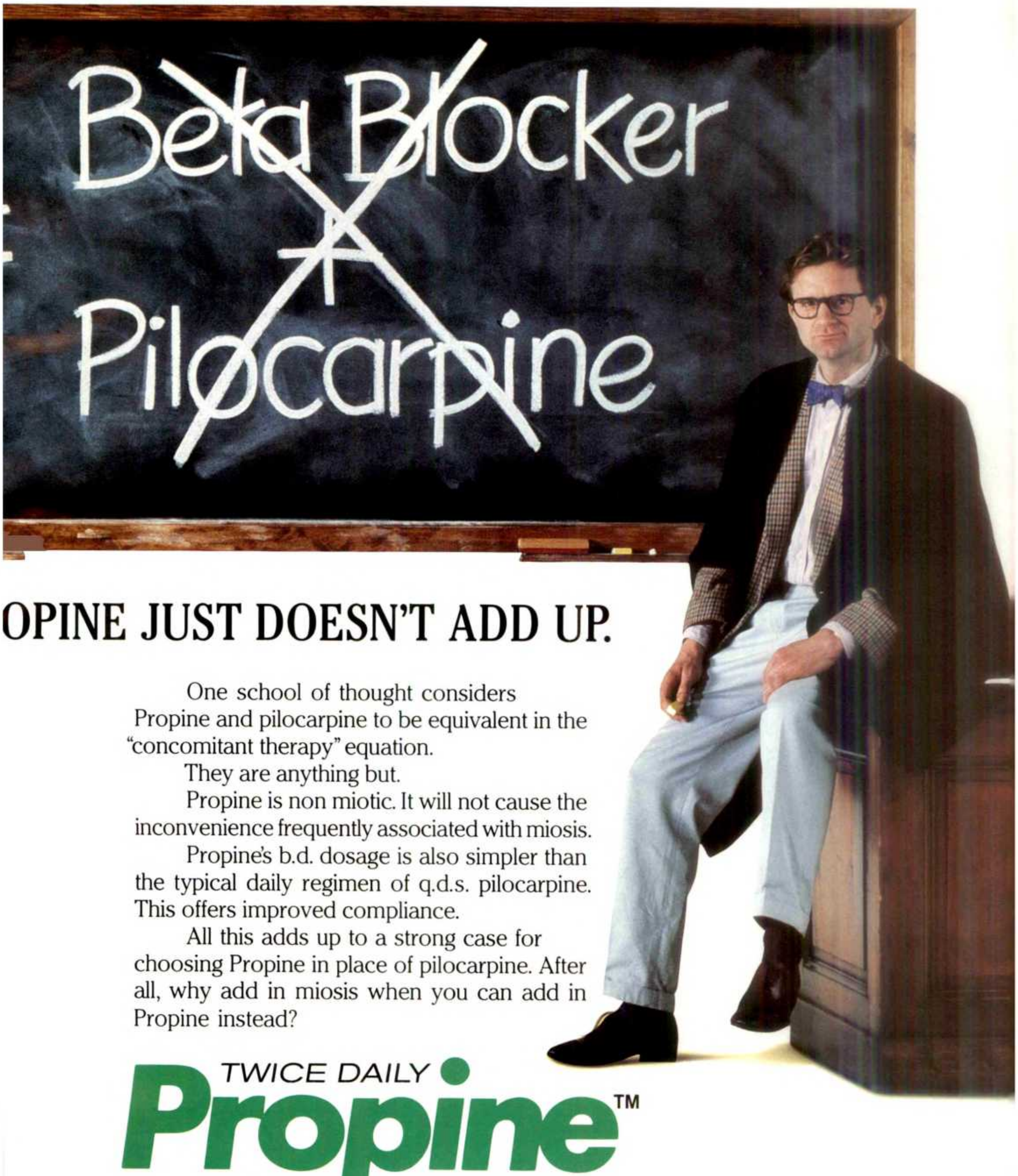

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*British Journal of Ophthalmology*, 1991, 75, 471–472

# Complete infarction of the eye complicating a choroidal malignant melanoma

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**Abstract**

**Infarction of malignant melanoma of the choroid has been previously reported, but infarction of the whole eye in association with infarction of melanoma is a rare event that has not been previously described. We present such a case and discuss the possible pathogenesis.**

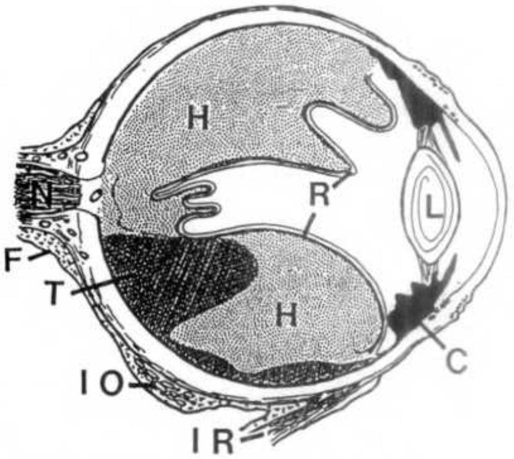

*Figure 1 A diagram of a parasagittal section of the eye showing the location of the tumour* (T), *the detached retina* (R), *and retroretinal haemorrhage* (H). *The florid fibroblastic reaction extends from the region of the optic nerve* (F) *deep to the insertion of inferior oblique* (IO) *and into the tendon of the inferior rectus* (IR). *Optic nerve* (N), *lens* (L), *ciliary body* (C).

Choroidal malignant melanoma is the commonest intraocular tumour in adults, becoming more frequent with increasing age.[1] Such tumours are known to undergo partial or complete infarction, and various autoimmune mechanisms have been postulated.[2-4] In the present case infarction of a choroidal melanoma was associated with infarction of most of the globe.

## Case report

An 83 year old man presented to the casualty department of Southampton Eye Hospital complaining of blurred and distorted vision in the right eye for several weeks. Fundal examination revealed a large, inferotemporal pigmented mass extending to the optic disc with an associated exudative retinal detachment. Ultrasonography of the right eye confirmed a solid lesion, which was presumed to be primary choroidal malignant melanoma. The left fundus was normal. General examination, full blood count, erythrocyte sedimentation rate, liver function tests, and chest *x* ray revealed no abnormality.

He elected to be managed conservatively and was to be reviewed in three months. Two months later, however, he returned to the casualty department complaining of a three-day history of deteriorating vision in the right eye culminating in severe pain and complete loss of vision (no perception of light). The intraocular pressure was 70 mmHg, with corneal oedema and a fixed, dilated, oval pupil. A diagnosis of glaucoma secondary to choroidal malignant melanoma was made. The eye was enucleated four days later, by which time the anterior chamber had developed a total hyphaema. Postoperative recovery was uneventful. Three months' follow-up revealed no recurrent tumour.

### PATHOLOGY

Macroscopic inspection of the eye sectioned parasagittally revealed a completely detached retina with retroretinal haemorrhage. Dense connective tissue was adherent to the outside of the eye posteriorly.

Histological preparations showed a pigment-containing malignant melanoma arising from the region adjacent to the optic disc and extending midway into the vitreous chamber. The retina was detached partly by tumour and partly by haemorrhage (Fig 1). Fresh blood filled the

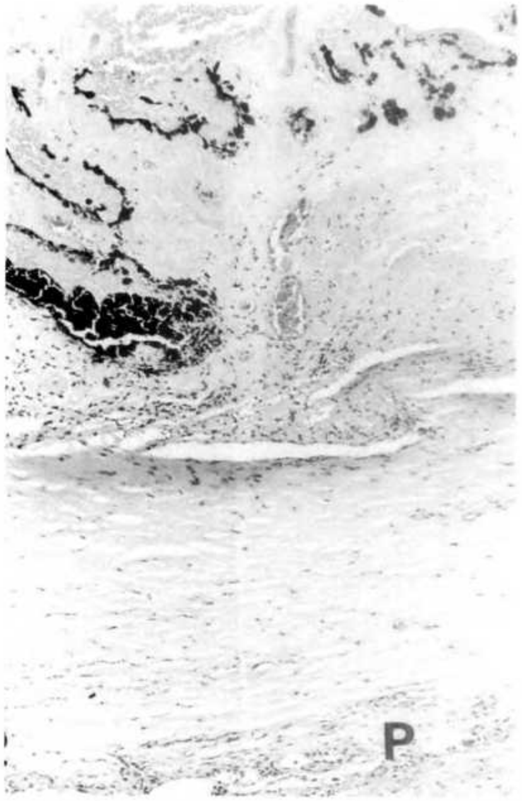

*Figure 2 Infarcted ciliary body (top) and sclera. The outer third of the sclera shows a polymorphonuclear leucocyte infiltrate* (P). (*Haematoxylin and eosin,* ×60.)

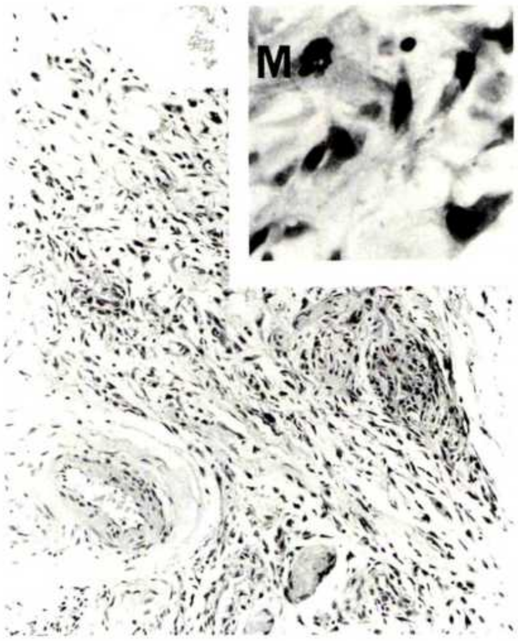

*Figure 3 Connective tissue around the optic nerve and ciliary arteries showing the prominent fibroblastic reaction. Inset: illustrates the bizarre nature of the cells and a mitotic figure* (M). *(Haematoxylin and eosin, ×85, inset ×215.)*

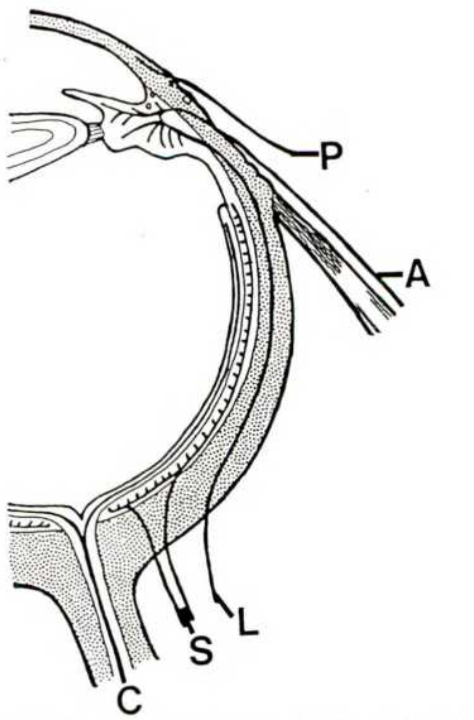

*Figure 4 Diagram of the arterial supply to the eye. Central retinal artery* (C). *Short* (S) *and long* (L) *posterior ciliary arteries pass circumferentially around the eye and could have been occluded by high intraocular pressure, thus causing infarction of intraocular structures in the present case. Anterior ciliary artery* (A) *and posterior conjunctival arteries* (P).

anterior chamber, and the lens showed cataractous change. No anterior synechiae were seen, and no cell debris could be identified in the trabecular meshwork.

Except for the cornea, all intraocular structures were totally necrotic, and they could be identified only by ghost-like profiles of the original cells (Fig 2). The inner two-thirds of the sclera was necrotic and acellular, and a band of pyknotic polymorphonuclear leucocytes was seen in the outer third of the sclera (Fig 2). Somewhat bizarre stellate and elongated cells with abundant slightly basophilic cytoplasm and large hyperchromatic nuclei with occasional mitoses were seen in the extraocular adipose tissue round the optic nerve (Fig 3). Such cells extended as a thin layer deep to the scleral attachment of the inferior oblique muscle and were seen throughout the tendon of the inferior rectus muscle. Although separated by the intervening sclera, the bizarre cells were related to the choroidal attachment of the necrotic malignant melanoma. These bizarre cells could, however, be distinguished from malignant melanoma cells by the absence of S100 protein expression immunohistochemically and by the lack of melanosomes on electron microscopy. From their distribution round the eye and their histological characteristics the bizarre cells were identified as a particularly florid fibroblast reaction to the ocular infarction.

No evidence of vasculitis or intravascular thrombi was detected in vessels of the sclera, optic nerve, or periocular tissue.

## Discussion

Although infarction of malignant melanomas of the choroid is well documented,[2] total infarction of the eye with a malignant melanoma has not, to the best of our knowledge, been described previously. The mechanism for infarction in this case is unclear. As multiple arteries supply the eye (Fig 4), infarction is not likely to be due to arterial embolic occlusion. Lack of vascular congestion and massive haemorrhage argue against venous infarction. From the history it appears that vision failed seven days before the eye was removed. It seems probable that a combination of glaucoma and infarction of the malignant melanoma resulted in a massive rise in intraocular pressure (measured at 70 mmHg). At such a pressure it is possible that the choroidal arteries on the inner aspect of the sclera (Fig 4) were compressed, resulting in infarction of virtually all the intraocular structures.

The major pathological feature, apart from the necrosis, was the florid fibroblast proliferation in connective tissue round the optic nerve and attachments of the inferior oblique and inferior rectus muscles. Despite the bizarre nature of some of the fibroblasts they could be distinguished from metastatic melanoma cells by immunohistochemistry and electron microscopy. The fibroblast reaction suggests that infarction of the eye occurred five to seven days before enucleation, the time when vision started to fail.

The authors express their appreciation to Miss M Harris for secretarial help in preparation of this manuscript.

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# Interferon-γ and tumour necrosis factor induce expression of major histocompatibility complex antigen on rat retinal astrocytes

Ahmed M Abu El-Asrar, Davide Maimone, Peter H Morse, Chris Lascola, Anthony T Reder

**Abstract**

**Cultured rat retinal astrocytes were tested by indirect immunofluorescence staining for their ability to express class I and II major histocompatibility complex (MHC) antigens under basal culture conditions and after three days of stimulation with two recombinant cytokines, rat interferon-γ (IFN-γ) and human tumour necrosis factorα (TNFα). Under basal culture conditions low levels of class I antigens were detected on a small percentage of cells, but there was no visible class II. IFN-γ and TNFα stimulation enhanced class I expression. TNFα had no effect on class II expression, whereas IFN-γ induced the expression of class II in a dose dependent manner. These findings suggest that retinal astrocytes might play a part in immunological events occurring in the retina.**

The retina, like the central nervous system, is considered immunologically privileged because of the presence of a blood-retina barrier and the lack of lymphatic drainage. Nevertheless, it can be the target of immune mediated reactions such as diabetic retinopathy, retinal vasculitis,[1] experimental autoimmune uveoretinitis,[2-4] viral infections such as herpes simplex, varicella zoster, cytomegalovirus, and toxoplasmic retinitis. Recent work has demonstrated that brain astrocytes are involved in immunological events occurring in the central nervous system.[5-8] The immune functions of retinal astrocytes, however, have not been studied. Some authors suggest that they are not essential for any retinal function.[9]

Major histocompatibility complex (MHC) antigens play an important part in the initiation of immune responses, and their expression on retinal astrocytes could trigger or facilitate immune functions in the retina. Class II MHC antigens, recognised by CD4 helper and CD4 cytotoxic T cells, are necessary for antigen presentation and for limited cytotoxic cell functions. Class I MHC antigens are recognised on target cells by CD8 cytotoxic cells, which constitute the majority of cytotoxic T cells in vivo.[10-13]

Cytokines, secreted by lymphocytes and macrophages, serve as soluble mediators of immune cell activity and can regulate their expression of MHC molecules. Among these cytokines, interferon-γ (IFN-γ)[5 14-16] and tumour necrosis factorα (TNFα)[17-20] induce class I and II MHC antigens on a variety of cell types in vitro.

In order to understand the pathogenesis of retinal immune-mediated diseases, it is necessary to identify factors that enhance MHC antigen expression on retinal cells. We examined the effect of the cytokines IFN-γ and TNFα in inducing the expression of MHC antigens on cultured rat retinal astrocytes.

## Materials and Methods

### RECOMBINANT PROTEINS AND ANTIBODIES

Rat recombinant IFN-γ was purchased from Amgen Biologicals (Thousand Oaks, CA, USA), and recombinant human TNFα was obtained from Knoll Pharmaceuticals (Whippany, New Jersey, USA). Rabbit monoclonal antibody to human glial fibrillary acidic protein (GFAP) was obtained from Chemicon International (Temecula, CA, USA), and mouse monoclonal antibodies to rat class I and II MHC (polymorphic) antigens were purchased from Serotec (Oxford, UK). Secondary antibodies were fluorescein-conjugated goat anti-mouse IgG from Cappel Laboratories (Malvern, PA, USA), and fluorescein-conjugated goat anti-rabbit IgG from Tago (Burlingame, CA, USA).

### CULTURE CONDITIONS

Retinas were dissected from the eyes of postnatal day 1 Holtzman rats under sterile conditions with the aid of a stereomicroscope, placed in culture medium, and mechanically dissociated by trituration through progressively smaller needles. A suspension of approximately $2\times10^6$ cells in 1·5 ml of culture medium was added to each poly-L-lysine (50 mg/l)–coated 35 mm Petri dish (Falcon). The culture medium was Dulbecco's modified Eagle's medium (DME) (Sigma Chemical Company, St Louis, MO, USA) supplemented with 10% heat inactivated calf serum, penicillin (20 units/ml), and streptomycin (20 mg/ml). Cultures were incubated at 37°C in a humidified atmosphere of 5% carbon dioxide-95% air. The growth medium was changed twice weekly. Three-week-old cultures were used throughout this study.

Astrocytes were identified by the presence of cytoplasmic glial fibrillary acidic protein, an intracellular antigen unique to astrocytes.[21] The cells were fixed for 5 min in 5% acetic acid/ethanol on ice. A rabbit monoclonal antibody to human GFAP (1:50) was incubated with retinal cells for 30 min on ice, followed by a 30 min incubation with fluorescein-conjugated goat anti-rabbit IgG (1:20). The cells were then mounted with 60% glycerol in trometamol (tris) buffered saline, and visualised by fluorescent microscopy. Astrocyte cultures were >95% positive for GFAP (Fig 1).

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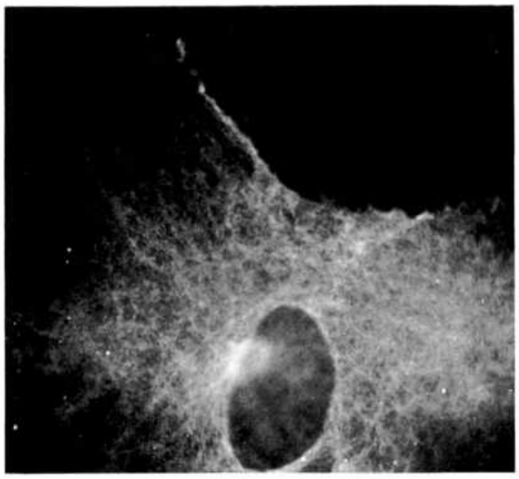

*Figure 1 A GFAP$^{+}$ retinal astrocyte. Cultures were >95% GFAP+. (Indirect immunofluorescence staining, ×800.)*

### IFN-γ AND TNFα TREATMENTS

Cultures were treated with IFN-γ (2–200 U/ml) or TNFα (50 μg/l) for three days before they were stained. For control purposes parallel cultures were maintained in the culture medium alone.

### INDIRECT IMMUNOFLUORESCENCE STAINING FOR CLASS I AND II MHC ANTIGENS

The cells were incubated for 20 min with 5% goat serum, followed by a 60 min incubation with monoclonal antibodies to rat class I (1:50) or class II (undiluted) determinants at 4°C. The cells were then washed three times with phosphate buffered saline (PBS) containing 1% bovine serum albumin and 0·02% sodium azide, followed by a 30 min incubation with fluorescein conjugated goat anti-mouse IgG (1:20) on ice. After being washed three times the cells were fixed for 10 min in 4% paraformaldehyde, mounted in 60% glycerol in trometamol buffered saline, and examined by inverted fluorescent microscopy (Leitz) ×1000. As controls some cultures were incubated with the washing solution in place of first antibody or with an irrelevant monoclonal antibody of the same isotype. Neither control displayed positive staining.

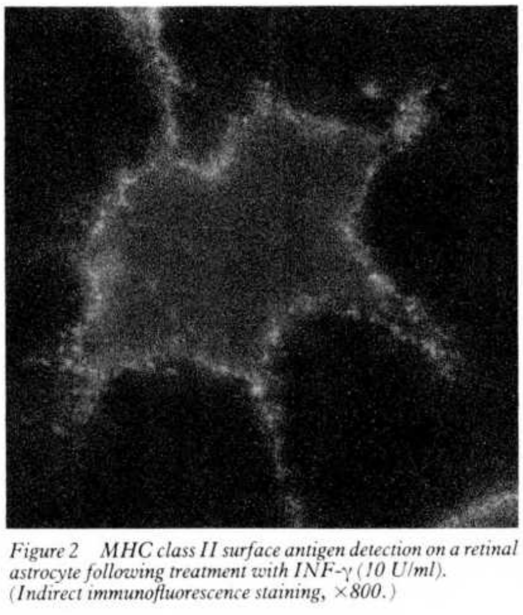

*Figure 2 MHC class II surface antigen detection on a retinal astrocyte following treatment with INF-γ (10 U/ml). (Indirect immunofluorescence staining, ×800.)*

## Results

Untreated cultured rat retinal astrocytes expressed low levels of class I MHC antigens in a small percentage of cells (<10%), whereas class II MHC antigens were not detected.

Recombinant IFN-γ treatment enhanced class I expression. The percentage of cells expressing class I increased from a baseline of <10 to >95%. Following exposure to IFN-γ at 2–200 U/ml. IFN-γ at 2 or 5 U/ml induced low levels of class II antigen synthesis by a few cells (<10%). Maximum expression by most of the cells (>95%) followed exposure to IFN-γ at 10–200 U/ml (Fig 2).

Recombinant TNFα at 50 μg/l induced high levels of class I antigens on most of the cells (>95%). On the other hand, TNFα had no stimulatory effect on class II antigen expression.

## Discussion

These data show that in rat retinal astrocytes under basal culture conditions low levels of class I MHC antigens are expressed by a few cells, but class II antigens are not expressed. IFN-γ enhances the expression of class I antigens and induces the expression of class II antigens. In addition, TNFα induces class I expression on the surface of retinal astrocytes, whereas class II expression is not affected by TNFα treatment.

Surface expression of MHC antigens is the molecular basis for antigen presentation.[14] Class II antigens are found on cells involved in immune responses, including B cells, activated human and rat T cells, and antigen presenting cells such as macrophages. The presence of class II antigens on these cells is associated with antigen recognition and presentation to T cells and the initiation of specific B and T cell responses.[22 23] IFN-γ from activated T cells is a potent inducer of both class I and II antigens on cells; brain astrocytes treated with IFN-γ also express class II antigens.[5] Brain astrocytes, on expression of class II antigens, can function as antigen presenting cells and present antigens such as myelin basic protein to specifically sensitised T cells.[6] By analogy with the brain, IFN-γ-induced expression of class II MHC antigens on retinal astrocytes could allow these cells to act as antigen presenting cells and in turn play a part in immunological events occurring in the retina.

Several studies have demonstrated close contact between retinal astrocytes and retinal vascular tissue.[24-26] Accordingly, active contact between the immune system and the retina may directly depend on astrocyte function and makes the astrocytes one of the first cells encountered by intruding T cells.

TNFα is produced by mononuclear phagocytes[27] and astrocytes[28] in response to inflammatory stimuli. It increases expression of class I MHC antigens on brain astrocytes,[29 30] but it has no effect on induction of class II MHC molecules. TNFα, however, augments class II induction on brain astrocytes in conjunction with virus infection[31] or IFN-γ.[19] Class I MHC antigens are particularly important for T cell recognition of virus antigens expressed on the surface of infected cells.[32] Brain astrocytes can be susceptible targets in vitro for class-I-specific cytotoxic T lymphocytes.[33] Accordingly, class I enhancement on retinal astrocytes induced by IFN-γ or TNFα may render these cells susceptible targets for class-I-restricted cytotoxic lymphocytes.

In conclusion, our data show that IFN-γ and TNFα induce MHC antigens on rat retinal astrocytes in culture. These cytokines could be released by activated immune cells recruited to the retina in response to a viral infection or during immune mediated diseases that cause breakdown of the blood-retina barrier. Class I enhancement could render retinal astrocytes susceptible targets for class-I-restricted cytotoxic T lymphocytes. In addition, once astrocytes express class II, they may function as antigen presenting cells and induce further expansion of T lymphocyte clones within the retina.

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# Comparison of the effects of intraocular irrigating solutions on the corneal endothelium in intraocular lens implantation

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## Abstract

**We conducted a randomised prospective controlled study to determine the effects of a glucose glutathione bicarbonate solution (BSS Plus) and a citrate acetate bicarbonate solution ($S\text{-}MA_2$) on the corneal endothelium in patients undergoing extracapsular cataract extraction with posterior chamber lens implantation. One eye of each patient was randomly assigned to receive BSS Plus, and the other eye to receive $S\text{-}MA_2$. BSS Plus caused significantly less corneal swelling on the first postoperative day than did $S\text{-}MA_2$. There was no difference between the two solutions in their effect on corneal thickness one week and one month postoperatively. Computer assisted morphometric analysis of wide-field specular microscopic photographs demonstrated minimal changes in endothelial morphological characteristics in the eyes irrigated with BSS Plus. By comparison $S\text{-}MA_2$, caused a significant loss of endothelial cells and a marked reduction in the figure coefficient. These results indicated that BSS Plus has a clinical advantage over $S\text{-}MA_2$ with respect to the corneal endothelium.**

With the development of sophisticated intraocular surgical techniques, there is an increasing need for commercially available intraocular irrigating solutions that can maintain the integrity of the corneal endothelium and other intraocular tissues even when used in a large volume and for a long time period. Previous in-vitro perfusion studies have shown that normal saline, Plasmalyte 148, lactated Ringer's solution, and balanced salt solution (BSS) are toxic to the corneal endothelium.[1,2] These studies have also shown that maintenance of endothelial integrity can best be obtained by use of glutathione bicarbonate Ringer's solution (GBR), which is similar in chemical composition to that of aqueous humour.[1-4] However, GBR is not suitable for clinical use, since it is chemically unstable once made up.

Two intraocular irrigating solutions have recently become commercially available (Table 1). They are BSS Plus,[5] a glucose glutathione bicarbonate solution, and $S\text{-}MA_2$[6,7] a citrate acetate bicarbonate solution. BSS Plus is similar to GBR except for lacking adenosine and having an addition of oxidised glutathione instead of reduced glutathione. $S\text{-}MA_2$ is also similar to GBR except that citrate and acetate are added, and glutathione and adenosine are lacking from the medium. Previous experimental studies[5-8] and clinical trials[9-12] have demonstrated that both solutions are more effective in preventing corneal swelling and maintaining the structure of the corneal endothelium than either lactated Ringer's solution or BSS.

Which irrigating solution, BSS Plus or $S\text{-}MA_2$, is better for the corneal endothelium is of great importance. Recent experimental studies on rabbit, cat, and human donor corneas have consistently shown that $S\text{-}MA_2$ may be more harmful to the endothelium than BSS Plus.[13,14] Consequently this randomised prospective controlled study was undertaken to determine whether there is a difference between BSS Plus and $S\text{-}MA_2$ concerning the effects on the corneal endothelium in patients undergoing posterior chamber lens implantation.

## Materials and methods

We studied 21 patients with senile cataract scheduled for extracapsular cataract extraction with posterior chamber lens implantation. The age of the patients ranged from 58 to 88 years (mean, 74 years). Informed written consent was obtained from each patient. Both eyes of each patient were operated on by one surgeon with the same technique and medications. The operations were performed at one-week intervals. One eye of each patient was randomly assigned to receive BSS Plus and the other eye to receive $S\text{-}MA_2$.

A complete ocular examination was performed on all patients. We excluded patients with a history of ocular trauma, surgery, or contact lens wear. Patients with systemic disease, such as diabetes and cystic fibrosis, or ocular conditions that might affect the corneal endothelium, such as uveitis, pseudoexfoliation syndrome, and glaucoma, were also excluded, as were patients with low cell densities or morphological abnormalities of the endothelium preoperatively. Only

*Table 1 Chemical composition of GBR, BSS Plus, and $S\text{-}MA_2$*

| *Constituent* | *GBR* | *BSS Plus* | *$S\text{-}MA_2$* |
|---|---|---|---|
| Sodium chloride | 111·6 | 122·2 | 112·9 |
| Potassium chloride | 4·8 | 5 08 | 4 8 |
| Calcium chloride | 1·1 | 1 05 | 1 2 |
| Magnesium chloride | 0·78 | 0·98 | – |
| Magnesium sulphate | – | – | 1 2 |
| Sodium acetate | – | – | 4·4 |
| Sodium citrate | – | – | 3·4 |
| Sodium acid phosphate | 0·86 | – | – |
| Disodium phosphate | – | 3·0 | – |
| Sodium bicarbonate | 29·2 | 25·0 | 25 0 |
| Dextrose | 5·01 | 5·11 | 8·3 |
| Glutathione (reduced) | 0·30 | – | – |
| Glutathione (oxidised) | – | 0·30 | – |
| Adenosine | 0·50 | – | – |
| pH | 7 4 | 7·4 | 7·3 |
| Osmolarity (mOsm) | 274 | 305 | 290 |

All concentrations expressed in mmol/l of solution patients with neither surgical nor postoperative complications were included in the study.

A standard surgical technique was used on all patients. We made a fornix-based conjunctival flap and limbal incision of a 10 mm arc length and filled the anterior chamber with 1% sodium hyaluronate. After anterior capsulotomy with a bent 23 gauge needle the lens nucleus was expressed by a two-point compression without collapse of the corneal dome. We then performed a cortical clean-up with an aspiration-irrigation instrument, followed by expansion of the capsular bag with 1% sodium hyaluronate, insertion of posterior chamber lens in the capsular bag, and aspiration of the viscoelastic substance. The wound was closed with five to seven interrupted 10–0 nylon sutures. No epinephrine was added to the irrigating solutions or injected into the anterior chamber. At the end of surgery 0·1 to 0·6 ml of acetylcholine chloride was injected into the anterior chamber. Postoperative medications, including topical antibiotics and corticosteroids, were given in the same fashion to all patients.

Central corneal thickness was measured preoperatively and at one day, one week, and one month after surgery. A Haag-Streit slit-lamp with a pachymeter fitted with central fixation lights, according to Mishima and Hedbys,[15] is used for these measurements. The use of these fixation lights is essential in order to obtain consistent measurements of central thickness. Each time the average of three consecutive readings was recorded. The endothelium of the central cornea (3 to 4 mm in diameter) was also photographed with a wide-field specular microscope preoperatively and at one week and one month after the operation. Specular microscopy during the first postoperative week was not performed in order to keep the eyes as sterile as possible.

Approximately 10 to 15 photographs were taken of each cornea. Adequate photographs were obtained from each eye of the 21 patients at all examinations. The photographs with good resolution were used for analysis. A total of 100 adjacent cells were analysed with a computerised digitiser, as previously described.[16,17] Corneal pachymetry, endothelial photography, and morphological evaluation were performed by independent examiners who were unaware of which irrigating solution was used for any eye until the entire study was completed.

*Table 2 Clinical data and preoperative endothelial morphology: mean (SEM)*

| | *BSS Plus group (n=21)* | *S-MA$_2$ group (n=21 paired eyes)* |
|---|---|---|
| Irrigation time (min) | 8.9 (1·0) | 10·0 (1·7) |
| Infusion volume (ml) | 97·1 (12·8) | 97·4 (12·1) |
| Corneal thickness (mm) | 0·53 (0·008) | 0·53 (0·008) |
| Endothelial morphology | | |
| Cell density (cells/mm$^2$) | 2900 (89) | 2961 (125) |
| Coefficient of variation* | 0·330 0·298, 0·390 | 0·314· 0·276, 0·348 |
| Hexagonal cells (%) | 58·3 (1·7) | 61·0 (1·7) |
| Figure coefficient | 0·850 (0·002) | 0·852 (0·002) |

*Median quartile

Endothelial cell density (cells/mm$^2$) was calculated by dividing $10^6$ by the mean cell area. Cell loss was expressed as a percentage of the preoperative cell density. The coefficient of variation in cell size (SD expressed as a ratio to the mean cell area) was used as a quantitative measurement of cell size variability (polymegethism). Cell shape was defined by the number of apices of each cell. The percentage of hexagonal cells was used to describe cell shape variability (pleomorphism). The figure coefficient was also calculated by the formula of $4\pi A/P^2$, where A is the cell area and P is the total perimeter. This factor is a dimensionless index describing the degree to which a cell approximates to a circle. The value of this index is 1·0 for a perfect circle and 0·907 for a perfect hexagon. The figure coefficient was used to quantify the degree to which the endothelial monolayer deviates from its normal hexagonal patterns.

Differenees were considered statistically significant if parametric (two-tailed paired *t* test) and non-parametric (two-tailed Wilcoxon one-sample test) tests yielded a p value of less than 0·05.

## Results

There were no significant differences in amount of irrigating solution or irrigation time between the eyes receiving BSS Plus and those receiving S-MA$_2$ (Table 2). These two groups were also equivalent with respect to all the baseline variables, including corneal thickness, endothelial cell density, coefficient of variation in cell size, percentage of hexagonal cells, and figure coefficient.

In both the BSS Plus and S-MA$_2$ groups the corneal thickness increased significantly over the baseline values one day after surgery and steadily decreased with time (Fig 1). The corneal thickness on day 1 was significantly greater in the S-MA$_2$ group than in the BSS Plus group. There was no significant difference in corneal thickness between the two groups one week and one month after surgery. One month postoperatively, the corneal thickness returned to the baseline values in the BSS Plus group, while it was significantly increased from the preoperative value in the S-MA$_2$ group.

The eyes receiving S-MA$_2$ had a significant endothelial cell loss from the baseline one week and one month after surgery, whereas those with BSS Plus did not (Fig 2). The mean cell losses were higher for the S-MA$_2$ group than for the BSS Plus group at any point in time, though this difference was statistically insignificant. The coefficient of variation in cell size and percentage of hexagonal cells remained unchanged from the baseline values in both groups. The S-MA$_2$ group demonstrated a significant decrease in the figure coefficent compared with the baseline value and with the BSS Plus group one month after surgery. No change in the figure coefficient was noted in the BSS Plus group.

## Discussion

The results of this randomised prospective controlled study demonstrated that BSS Plus offers a significant clinical advantage over S-MA$_2$ with respect to the corneal endothelium in

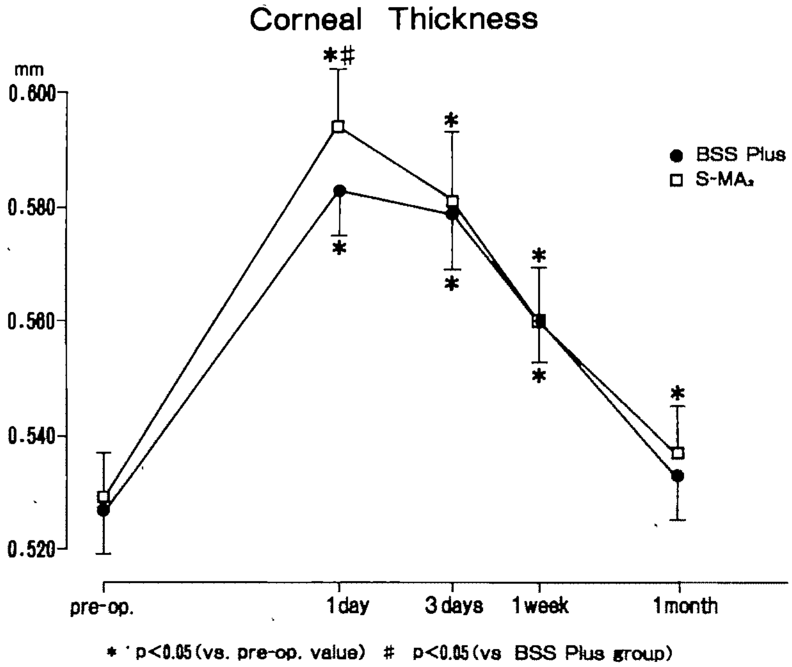

*Figure 1 Central corneal thickness in the eyes receiving BSS Plus or S-MA$_2$. Each point represents the mean; bars represent SEM. *Significantly different ($p<0{\cdot}05$) from the baseline value. #Significantly different ($p<0{\cdot}05$) compared with the BSS Plus group.*

patients undergoing extracapsular cataract extraction with posterior chamber lens implantation. The eyes receiving BSS Plus had less corneal swelling and fewer endothelial morphological changes than the paired eyes receiving S-MA$_2$.

Araie[15] recently showed that S-MA$_2$ perfusion substantially increased the permeability of carboxyfluorescein to the rabbit corneal endothelium, while BSS Plus did not. In an in-vitro perfusion of human donor corneas Edelhauser[14] has also noted that S-MA$_2$ caused more corneal swelling than BSS Plus and a marked breakdown of the endothelial cell junctions, which is similar to what occurs in calcium-free medium,[12 18 19] whereas BSS Plus maintained the functional and structural integrity of the endothelium. These observations suggest that a significantly greater corneal thickness noted in our patients with S-MA$_2$ one day after surgery may be due at least in part to compromised endothelial barrier function.

In our study none of the morphological parameters changed significantly from the baseline values in the eyes receiving BSS Plus. By comparison a significant cell loss from the baseline was noted in the paired eyes receiving S-MA$_2$. The S-MA$_2$ group also showed a marked decrease in the figure coefficient one month after surgery, indicating a loss of the normal hexagonal pattern. However, no significant change was noted in the coefficient of variation in cell size (polymegethism) or percentage of hexagonal cells (pleomorphism). A recent study has also demonstrated that in-vivo irrigation of the anterior chamber in cats with S-MA$_2$ caused marked endothelial morphological changes (polymegethism and pleomorphism), while BSS Plus did not.[14] These endothelial changes were found to be present during the early postoperative period and to resolve within one week after the irrigation. Since we took the first endothelial photographs one week after surgery, significant increases in polymegethism and pleomorphism caused by S-MA$_2$ might not have been detectable.

The normal corneal endothelium is a densely packed monolayer with a regular hexagonal pattern. A regular hexagonal shape (given a

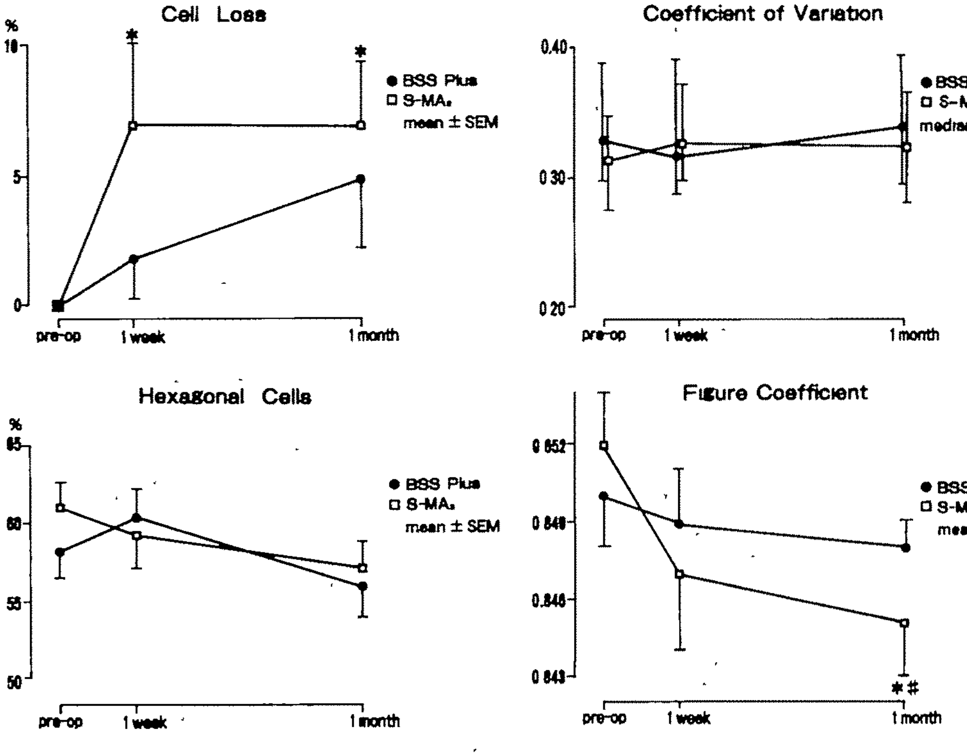

*Figure 2 Endothelial cell loss (top left), coefficient of variation in cell size (top right), percentage of hexagonal cells (bottom left) and figure coefficient (bottom right) in the eyes receiving BSS Plus or S-MA$_2$. *Significantly different ($p<0{\cdot}05$) from the baseline value. #Significantly different ($p<0{\cdot}05$) compared with the BSS Plus group.*

constant area) is the most geometrically or thermodynamically stable configuration to cover a plane,[20–22] because this shape will keep the total perimeter at a minimum, and thus produce the minimum surface tension energy. Therefore it can be proposed that a marked disruption of regular hexagonal pattern noted after S-MA$_2$ irrigation represents an endothelium in a physically unstable state,[16,23] which may be more susceptible to additional trauma. Morever, a loss of regular hexagonal pattern may reflect cell loss, causing adjacent cells to assume irregular hexagonal or elongated shapes (given a constant area) to cover the cell free area.[16,23]

The difference between BSS Plus and S-MA$_2$ is that S-MA$_2$ lacks glutathione and contains sodium acetate and citrate. Oxidised or reduced glutathione, which are present in the aqueous humour[24] and corneal endothelium,[25] have been shown to be important for the maintenance of endothelial cell junctions and barrier function.[1,3,4,26–28] Since acetate and citrate are unnatural buffers to the intraocular tissues, they may have some adverse effects on the endothelium.[13,14] In addition there is a possibility[13,14] that citrate may chelate calcium in the solution and decrease an amount of free $Ca^{2+}$, which is essential for maintaining endothelial junctional complexes and barrier function.[1,2,18,19] Therefore the lack of glutathione, presence of acetate and citrate, and possible loss of free $Ca^{2+}$ in S-MA$_2$ may all be responsible for the endothelial alterations observed in both previous experimental investigations[13,14] and the present clinical study.

Our results indicated that BSS Plus is more effective in protecting the functional and structural integrity of the corneal endothelium than S-MA$_2$ in patients undergoing posterior chamber lens implantation. The ability of BSS Plus to maintain endothelial integrity can be attributed to its chemical similarity to aqueous humour. Patients with low cell densities or morphological abnormalites of the endothelium have been shown to be more susceptible to surgical trauma and to a variety of stresses.[16,29–33] The use of BSS Plus may be preferable and safer in this group of high-risk patients.

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# Eyedrop instillation for reluctant children

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## Abstract

**Pupillary responses to pilocarpine eyedrops applied by different techniques have been studied in healthy volunteer subjects. In particular a novel method was evaluated in which eyedrops were applied to the inner canthus with eyes tightly closed and the subject supine, followed immediately by opening of the eyes. The response to this technique indicates that drug penetration into the eye was 66% (confidence intervals 28 to 104%) of that obtained by conventional instillation, into the conjunctival sac, with or without 2 min pressure on the inner canthus. This method of instillation, which is free of aggravation, may be clinically useful for patients, especially children, unwilling or unable to tolerate conventional instillation.**

It is everyone's experience that some children are resolute in their refusal to submit to instillation of eyedrops. Overcoming this resolve is traumatic for the patient, parents, nursing staff, and ophthalmologist alike. The author's personal experience as an affected parent led to the present experiments, designed to explore the efficacy of a less traumatic mode of instillation suitable for use in children.

The method involves placing eyedrops on the inner canthus with the subject lying supine and with eyes tightly closed. Once the eyedrops are in place the subject is instructed to open his or her eyes, allowing the eyedrops to enter the eye.

The investigation reported here was designed to measure the efficacy of this method by comparison with conventional modes of administration. Pilocarpine was used as marker and its miotic effect as a measure of its penetration into the eye. The observations were made on young healthy adults, because such experiments on children are considered unethical.

## Subjects and methods

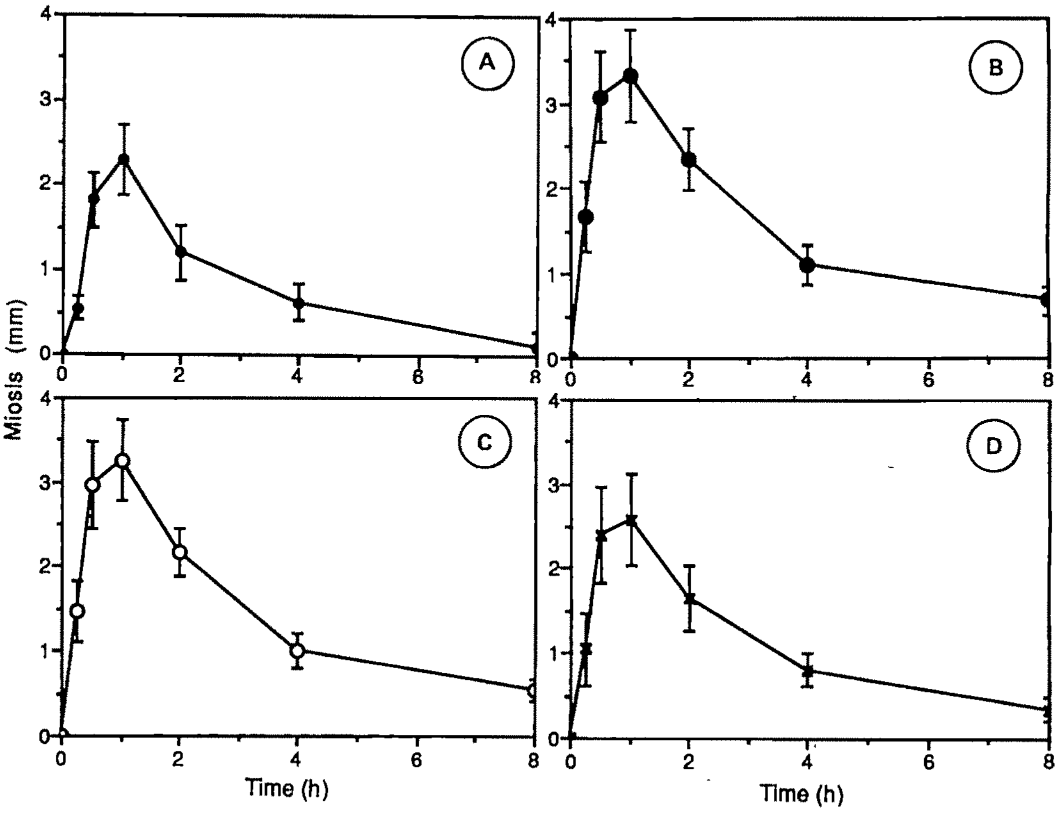
Ten healthy subjects (6M, 4F) aged 20 to 33 years took part in the study. Each attended on four occasions at least three days apart and received a single eyedrop (0·037 ml) of pilocarpine nitrate in one eye by each of the following methods in balanced order:

pilocarpine 0·25% with pressure on the inner canthus;

pilocarpine 0·5% with pressure on the inner canthus;

pilocarpine 0·5% without pressure;

pilocarpine 0·5% to inner canthus with eyes closed.



*Miotic response (mean (SEM)) to pilocarpine following different methods and doses of administration. A: 0·25% with pressure on the inner canthus. B: 0·5% with similar pressure. C: 0·5% without pressure. D: 0·5% with eyes closed.*

All eyedrops were made up by dilution of pilocarpine 2% Minims in phosphate buffer pH 7·0. With all but the last method the eyedrops were placed in the conjunctival sac. In the first two methods digital pressure on the inner canthus was maintained for 2 min.

Measurements of darkness pupil diameters of both eyes were made by infrared TV pupillography[1] before and at 15 and 30 min and 1, 2, 4, and 8 h after drug instillation. The miotic response was defined as the difference in pupil diameter between treated and untreated eyes, corrected for any diameter difference before treatment, and expressed both as peak values and as areas under the response curves. The relative efficacy of the different modes of administration was assessed by reference to the dose response relationship found with pressure on the inner canthus as previously reported.[2]

Each subject gave written consent to participation, and the study was approved by the Ethics Committee of West Lambeth Health Authority.

## Results

The time courses of miotic responses to the four treatments are shown in the figure, the peak and area under the response curves (AUC) in the Table. With digital pressure on the inner canthus significantly larger peak and AUC responses were obtained with 0·5% than with 0·25% pilocarpine ($p=0·029$ and 0·010 respectively from paired *t* tests). Without such pressure pilocarpine 0·5% responses did not differ significantly from those obtained with pressure, and the overall mean comparative bioavailability was 94·1% on peak response and 88·8% on AUC.

Instillation of the same dose to the inner canthus with eyes closed produced responses intermediate between those obtained with 0·25% and 0·5% with pressure on the inner canthus but not differing significantly from either. The overall mean bioavailability was 64% on peak response and 62·5% on AUC. The times to peak response (30 min to 1 h) were identical.

*Peak responses and areas under the response curves (AUC) (mean (SEM)) to pilocarpine by different methods and dose of application. Pressure=2 min pressure applied to the inner canthus*

| Method | Concentration | Peak Response (mm) | AUC (mm h) |
|---|---|---|---|
| A With pressure | 0·25% | 2·32 (0·41) | 6·46 (1·73) |
| B With pressure | 0·5% | 3·47 (0·53) | 12·30 (2·01) |
| C Without pressure | 0·5% | 3·37 (0·48) | 11·31 (1·30) |
| D Eyes closed | 0·5% | 2·73 (0·53) | 8·70 (1·92) |

Estimation of the confidence intervals for bioavailability was based on measurements in seven of the 10 subjects in whom clear dose response relationships could be established. These limits, based on peak responses, were 25–117% (conjunctival sac) and 28–104% (inner canthus).

## Discussion

This study shows clearly that drug solution placed on the inner canthus with the eye closed subsequently penetrates the eye, albeit to a somewhat lesser extent than by the conventional mode of instillation into the conjunctival sac. The slight reduction was to be expected because the technique places the eyedrop close to the puncta, patency or occlusion of which is well-known to influence drug penetration.[3 4] Nevertheless sufficient bioavailability exists to suggest that this method of giving eyedrops should be effective clinically. Casual observations by the author and two colleagues indicate that its use on patients unwilling or unable to submit to conventional instillation is devoid of aggravation.

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# Ocutome lensectomy: results and complications

R V Pearson, G W Aylward, R J Marsh

**Abstract**

**We describe the results and the complications encountered in 69 lensectomies performed via a limbal approach with the Ocutome vitrectomy instrument, in which it was the intention at surgery to maintain the integrity of the posterior capsule. After operation 87% improved in visual acuity, and 68% achieved 6/12 or better. The main early complications encountered were perioperative rupture of the posterior capsule and iris damage. The main late complications were postoperative thickening of the posterior capsule, retinal detachment, and bullous keratopathy. Of the eyes in which the posterior capsule remained intact after operation 17% developed thickening of the posterior capsule to a degree that required capsulotomy over a mean follow-up period of 50 months.**

In the past, congenital cataracts were treated surgically by such procedures as optical iridectomy, discission ('needling'), Ziegler through-and-through discission, intracapsular extraction, and linear extraction.[1-5] The results were often so poor, or the rate of complications so high, that many surgeons favoured a conservative approach.[1,5,6]

Scheie *et al*[7,8] reintroduced the aspiration technique for congenital cataracts and soft cataracts of any aetiology in individuals under 30 years of age (before the nucleus is firmly formed). In their procedure the posterior capsule remained intact at the end of the initial operation and was only surgically opened at a later date if it became so opaque as to interfere with vision. The vitreous was therefore minimally disturbed by the inital procedure. This saw a significant reduction in the number of complications, in particular retinal detachment. It is a relatively simple technique performed with inexpensive equipment, but does have the disadvantages that it has frequently to be followed by a number of operations to clear opacities from the posterior capsule,[9-12] cannot be employed with hard cortical and nuclear material,[13] and the correct management of vitreous loss is difficult with the incision and instruments used.[14]

With the introduction of vitreous infusion suction cutters lensectomy became possible, as lens matter could be cut as well as sucked. It was originally described as an operation in which the whole lens, including the anterior and posterior capsules, was removed. It can be performed via a limbal[15] or pars plana (or plicata)[16] approach, and the posterior lens capsule can be directly removed, left intact, or a fine needle capsulotomy performed at the end of the primary procedure.

The advantages of the anterior or limbal approach include better visualisation of instruments, the ability to perform a sphincterotomy before lensectomy in eyes with small pupils, and the use of small incisions which reduce the risk of vitreous loss, iris prolapse, and flattening of the anterior chamber during and after surgery and allow for rapid wound healing with earlier fitting of contact lenses.[17] Other advantages include the ability to preserve the posterior capsule and leave the vitreous undisturbed, but its chief advantage is the avoidance of damage to the retina (that is, dialyses and tears) by the introduction, withdrawal, and manipulation of instruments. Its main disadvantage is that fluid flow over the endothelium may be excessive.

The pars plana or plicata approach on the other hand avoids direct manipulation of, and a large volume of fluid flow across, the corneal endothelium and iris, and it allows immediate removal of lens particles which may fall into the vitreous.[16,18] However, dialyses and tears of the peripheral retina are a real risk adjacent to the entry sites, and incidences as high as 37% have been reported.[19] As there is no developed pars plana for the first few months of life, careful placement of the instrument probes is required to avoid a traumatic retinal detachment or ciliochoroidal detachment by infusion into the suprachoroidal space. The possibility of these complications has made the anterior approach through the limbus or cornea the usual one in infancy.[9]

Taylor[9] compared aspiration, in which the posterior capsule was left intact, and lensectomy, in which it was removed, in the treatment of congenital cataract. Following aspiration 19 of 28 eyes required repeated capsulotomy to maintain the pupillary area clear for refraction, while none were required following lensectomy. In a recent larger series the incidence of secondary procedures, most commonly a posterior capsulotomy, was higher in the group of eyes which had lens aspiration than in those which had lensectomy.[20] However, the incidence of postoperative posterior capsular opacification can vary with technique of extraction, age, and cataract aetiology, and indeed even the absence of the posterior capsule does not guarantee against secondary growth of lens epithelium, which may obstruct the visual axis.[21] Most authors[6,9,22] advocate a primary posterior capsulotomy or capsulectomy for surgery in the first year of life.

In lensectomy with rupture or removal of the posterior capsule the anterior vitreous is disturbed or damaged, and the effect of this on the postoperative incidence of retinal detachment is at present unknown. However, Shapland[23] and Cordes[24] found that, the more the vitreous was disturbed, the greater was the incidence of late retinal detachment following discission and linear extraction. Although unproved, leaving the posterior capsule intact should result in a

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reduction in the incidence of retinal detachment. In addition, perioperative damage to the retina is avoided, strands of vitreous to the wound are eliminated, the anterior vitreous face remains intact, and so the incidence of cystoid macular oedema may be reduced;[25-27] and, if glaucoma filtration surgery is required at a later stage, it will not be hampered by vitreous in the anterior chamber. Further, an intact posterior capsule allows a greater flexibility in choice of secondary intraocular lens implant, and, should the posterior capsule opacify, the trend from surgical to YAG laser capsulotomy has made its treatment less invasive.

Lensectomy has been proposed for the treatment of complicated cataracts secondary to uveitis.[17 28-33] Small pupils due to posterior synechiae can be enlarged, particularly in Still's disease, and, in the presence of chronic uveitis, some consider that the posterior capsule[28 29] and anterior vitreous[30 31] should be removed. A potential scaffold for future inflammatory membrane formation is thus removed and capsular thickening and the need for capsulotomy obviated. Others, using phacoemulsification, have achieved excellent visual results while maintaining an intact, but vigorously scraped, posterior capsule.[32]

The instruments used for lensectomy were originally designed for vitreous surgery.[34-36] The Ocutome became available in 1975 and we prefer it because of the common-(20)-gauge separate infusion and cutting probes, guillotine cutting action, reliability, adjustability, and overall simplicity.[37 38] In use the small incisions and separate infusion facility help to keep the intraocular environment steadier without leaks or excessive fluid flow through the eye. In successful cases only 5 ml of infusion fluid is required and often as little as 2·5 ml.

The Western Ophthalmic Hospital acquired one of the first Ocutomes in the United Kingdom and began lensectomy in 1977. We considered that using the Ocutome and employing a limbal approach with preservation of the posterior capsule had both practical and theoretical advantages over alternative techniques for the surgical management of cataract suitable for lensectomy. This series describes the results obtained and the complications encountered in 69 lensectomies performed in this way.

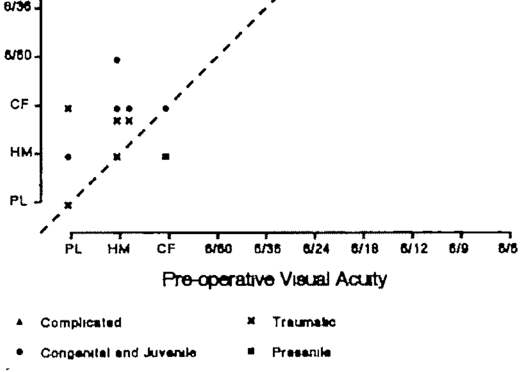

*Figure Relation of final to preoperative visual acuity.*

## Patients and Methods

One hundred and eight lensectomies were performed at the Western Ophthalmic Hospital over an eight-year period between July 1977 and October 1985. A retrospective study was performed with reference to the visual results obtained and the incidence of perioperative and postoperative complications. All information was obtained from the patients' hospital records. Cases were excluded for the following reasons: (1) previous intraocular surgery other than primary repair; (2) penetrating trauma involving the posterior segment, so eliminating the possibility of confusing the complications of these events with those of the lensectomy procedure itself; (3) cases where satisfactory follow-up was not available; (4) surgery performed with instruments other than the Ocutome.

The study group comprised 69 eyes (58 patients). Eleven patients had surgery performed on both eyes at different times. Thirty six patients were male and 22 were female, aged 1 to 65 years, mean 23 years. The period of follow-up ranged from 2 to 98 months, mean 50 months.

The cause of cataract in the 69 eyes studied was as follows: three eyes had complicated cataracts secondary to uveitis (including one with Reiter's syndrome); 32 eyes had congenital or juvenile cataract (including 1 associated with optic atrophy, 2 congenital dominant cataracts, and 2 associated wth retinopathy of prematurity); 27 cataracts were traumatic, 3 due to blunt and 24 due to penetrating trauma; 7 were presenile cataracts (including 4 myopic eyes). In 3 eyes cosmesis was the main indication for surgery, though it was expected that some improvement in visual field was to be achieved and possibly some enhancement of peripheral fusion, which may reduce the tendency towards strabismus.[39-41]

### OPERATIVE TECHNIQUE

All surgery was performed under general anaesthesia, following maximal pupillary dilatation.

A fixation knot manufactured from a 7·0 silk suture on a spatula point needle, inserted through superficial sclera 3 mm behind the limbus, was found useful for stabilisation of the eye when removing and introducing instruments. Stab incisions were made with an Ocutome stab blade at the temporal and nasal limbus. The anterior lens capsule was incised with the blade and hardness of the lens nucleus was then assessed by the ability of the knife to penetrate it. Failure, indicating too hard a nucleus for lensectomy, was followed by conversion of the operation to an extracapsular extraction. A separate infusion with a bent 20 gauge needle attached to a reservoir was inserted via the nasal stab incision.

Cortical lens matter was both directly aspirated and/or cut, the decision depending on the facility of aspiration. It was found inadvisable to engage and aspirate too much lens matter at once.

## Results

### VISUAL ACUITIES

The figure shows the preoperative to final visual acuity change. Only nine eyes (13%) had a preoperative visual acuity of better than 6/36. Forty seven eyes (68%) had a final acuity of 6/12 or better. In 60 eyes the visual acuity was improved, in five it was unchanged, and in one it was worse.

### COMPLICATIONS (Table)

*Early complications*

Perioperative rupture of the posterior capsule occurred in 21 eyes (30%). The relative risk of its occurrence was 1·88 in those with presenile cataracts compared with overall (zc=5·42, p<0·001). In one eye capsular rupture led to dislocation of the lens nucleus into the vitreous, which was immediately retrieved with the Ocutome.

Damage to the iris from accidental inclusion in the port of the Ocutome occurred in eight eyes. This produced minor cosmetic defects only.

The commonest postoperative complication was the presence of residual soft lens matter in the anterior chamber. The incidence of this was greater in the subgroup of traumatic cataracts. It was not associated with a reduction in visual acuity or an increased incidence of thickening of the posterior capsule.

Total hyphaema occurred in two eyes. One complicated cataract with extensive posterior synechiae showed complete resorption and a final visual acuity to 6/9. The other with cataract and disorganised anterior chamber secondary to penetrating trauma suffered organisation to form a fibrotic pupillary membrane, reducing the final visual acuity to perception of light. Bleeding from the iris was due to rupture of adhesions between it and other ocular structures which had formed secondary to trauma or inflammation.

*Table* *Numbers of complications*

| *Complication* | *Cataract type* | | | | |
|---|---|---|---|---|---|
| | *Complicated* | *Congenital and juvenile* | *Traumatic* | *Presenile* | *Total* |
| *Early complications* | | | | | |
| Posterior capsule rupture | – | 5 | 13 | 4 | 21 |
| Iris damage | – | 5 | 3 | – | 8 |
| Loss of lens material to vitreous | – | – | – | 1 | 1 |
| Dislocation of lens nucleus to vitreous | – | – | – | 1 | 1 |
| Hyphaema | 1 | – | 1 | – | 2 |
| Residual lens matter in AC | – | 1 | 9 | 1 | 11 |
| Total | 1 | 10 | 26 | 7 | 44 |
| *Late complications* | | | | | |
| Retinal detachment | – | – | 1 | 1 | 2 |
| Glaucoma | 1 | 1 | 1 | – | 2 |
| Posterior capsule | – | 5 | 1 | 2 | 8 |
| thickening iritis | 1 | – | – | – | 1 |
| Bullous keratopathy | – | – | 1 | 1 | 2 |
| Pupillary membrane | – | – | 1 | – | 1 |
| Total | 2 | 6 | 5 | 4 | 16 |

*Late complications*

Postoperative iritis recurred throughout a two-year follow-up in only one of three eyes with complicated cataract.

Retinal detachment occurred in two eyes postoperatively. One, with a dialysis in an eye with an intact posterior capsule, was detected two days after surgery for a cataract secondary to blunt trauma in a 34-year-old male. Successful detachment surgery resulted in a final visual acuity of 6/9. It is possible that this detachment was caused by the preceding trauma. The second occurred 13 months after lensectomy for a presenile cataract in a 46-year-old male, complicated by rupture of the posterior capsule and dislocation of the lens nucleus into the vitreous and its retrieval with the Ocutome. The retina, with lattice degeneration and atrophic holes, was flattened at surgery, but the acuity did not improve beyond hand movements.

Eight eyes developed opacification of the posterior capsule which required capsulotomy. Five of these, with a mean age of 20 years and range 10 to 31 years, were in the subgroup of congenital and juvenile cataracts. Final visual acuities were 6/9 or better in all eyes after surgical capsulotomy, and no eye required a repeat procedure. Three eyes underwent lensectomy, with preservation of the posterior capsule, for complicated cataract. None developed capsular thickening sufficient to require capsulotomy, and all had final visual acuities of 6/9 or better.

Bullous keratopathy ensued in two eyes. One occurred four years after lensectomy for a presenile cataract with a hard lens nucleus, necessitating its prolonged manipulation in the anterior chamber at surgery, resulting in endothelial damage. In the second eye corneal oedema did not clear after lensectomy in an eye with a cataract and leucoma adherens secondary to penetrating trauma in which the endothelium was noted to be compromised at the following primary repair.

Glaucoma developed postoperatively in two eyes. It was steroid induced in one eye with a complicated cataract and recurrence of iritis. In an eye with a juvenile cataract it occurred in presence of an open angle, unassociated with any pre- or postoperative complications and was successfully controlled with topical therapy. Both eyes have final visual acuities of 6/5.

### OPTICAL CORRECTION

Aphakia was initially corrected with contact lenses in 45 eyes (65%). Later nine of these 45 eyes become intolerant. Aphakic spectacles were used in 10 eyes (14%) initially and 16 eyes (23%) finally. Four myopic eyes achieved emmetropia, and 10 eyes initially and 13 eyes finally were ametropic and optically uncorrected. Five eyes were unable to benefit from their improved visual potential owing to contact lens intolerance in a unilaterally aphakic eye. None of the eyes in this study had a secondary intraocular lens inserted during the follow-up period.

## Discussion

Lensectomy through the limbus for juveniles and young patients with cataract proved to be a safe and successful operation. We preferred to preserve the posterior capsule if possible in all cases and achieved this in 70%. Only 17% of these required a posterior capsulotomy.

Leaving the posterior capsule intact avoids perioperative damage to the retina and causes minimal disturbance to the vitreous, eliminates strands of vitreous to the wound, and minimises and theoretically should eliminate lens matter falling into the vitreous. As secondary implantation of an intraocular lens may be increasingly considered at a later date in these eyes, this is a further indication for attempting to maintain the integrity of the posterior capsule, so increasing the safety of implantation and flexibility in choice of secondary intraocular lens. Indeed hopes for the future could include the development of flexible intraocular lenses inserted through the bore of 20 gauge instruments at the primary procedure and perhaps their removal and replacement by the same route to correct a change of refraction.

The main problem of leaving the posterior capsule intact, which has been well documented following aspiration[10–12] and phacoemulsification,[42] has been the high frequency, degree, and rapidity of its subsequent opacification. However, in our series leaving the posterior capsule intact, even in cases of congenital, juvenile, and complicated cataract, was followed by a low incidence of capsular opacification. Note should, however, be made of the lower mean age of the patients in the studies of Taylor *et al*,[9, 20] since postoperative thickening of the posterior capsule has been noted to occur more frequently and to develop more quickly in infancy[9] and particularly in juvenile chronic arthritis.[17]

If the posterior capsule does opacify, a posterior capsulotomy can now be performed, even in young patients with a YAG laser. The introduction of vertically aimed versions of these means that this treatment is becoming available to very young patients as a secondary procedure under a general anaesthetic.

We believe that lensectomy through the limbus is superior to the pars plana or plicata approach because it allows better visualisation of instruments, enables a sphincterotomy to be performed before lensectomy in eyes with small pupils, allows preservation of the posterior capsule and therefore causes minimal disturbance to the vitreous, and avoids damage to the peripheral retina by the introduction, withdrawal, and manipulation of and infusion through instruments.

Disadvantages and complications of lensectomy that have been described include failed lensectomy, loss of lens material into the vitreous, vitreous loss, vitreous haemorrhage, iris bleeding, iris damage, retinectomy, striate keratitis, retinal detachment, secondary pupillary membrane formation, and corneal endothelial damage. The main disadvantage of lensectomy is the unsuitability of the technique for removal of lenses with hard nuclei[17] and the large number of complications that occur when this is attempted.[13] Additional complications that we encountered include perioperative rupture of the posterior capsule and postoperatively the presence of residual soft lens matter in the anterior chamber, raised intraocular pressure, and recurrence of iritis.

We noted two retinal detachments in our patients. Although the first may have been caused by preceding blunt trauma, the second followed considerable manipulation of the vitreous to remove a dislocated lens nucleus, and we do know from earlier observations that the incidence of retinal detachment is higher if the vitreous is disturbed.[23, 24] Since retinal detachment has been reported as late as 33 years after congenital cataract surgery,[23, 43–46] a follow-up of this duration will be required to determine whether Ocutome lensectomy via an anterior approach with attempted preservation of the posterior capsule is associated with a lower (or higher) incidence of retinal detachment than that reported as following other operative techniques.[23, 47–50]

Endothelial damage and bullous keratopathy occurred when it was attempted to remove a cataract with a hard nucleus, necessitating its prolonged manipulation in the anterior chamber at surgery. The occurrence of this complication reflects bad case selection, and ways to avoid it include not attempting lensectomy on eyes with hard nuclei (that is, nuclear sclerosis) and assessing the degree of hardness of the lens nucleus preoperatively and converting to an extracapsular extraction if indicated. Similarly, the higher incidence of perioperative rupture of the posterior capsule in the subgroup of presenile cataracts could be reduced in the same way.

The treatment of choice for a cataract with any significant nucleus is extracapsular cataract extraction or phacoemulsification. Phacoemulsification has the advantage of a small (3 mm) incision, and with skillful handling can deal with quite dense nuclei. From the point of view of case selection patients under 30 years should perhaps be considered for lensectomy, as the incisions are smaller than for phacoemulsification, less fluid is infused through, and the instruments are not so difficult to manoeuvre in the eye. At age 30 or more elective phacoemulsification or extracapsular extraction are probably more appropriate.

Our thanks are due to the consultant surgeons of the Western Ophthalmic Hospital for permission to publish details of patients under their care and to the staff of the medical records department for their assistance

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# Surgical management of essential blepharospasm

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## Abstract

**We have reviewed the surgical management of essential blepharospasm over the last 15 years, comparing the results from facial nerve avulsion with those from orbicularis muscle stripping. After facial nerve avulsion 50% of patients remained free of troublesome spasm for 15 months after surgery, but only 25% remained so for more than two years. Following orbicularis oculi myectomy 50% of patients were free of troublesome spasms for 30 months after surgery and 55% of patients had relief from spasm for more than two years. Secondary effects of the two procedures are compared and are found to be fewer after orbicularis myectomy. There were no major complications after either form of surgery. Botulinum toxin is the treatment of first choice for this condition. If this becomes ineffective or inconvenient, surgical treatment is warranted and should not be deferred for fear of severe side effects of treatment, since these are rare. Protractor myectomy gives longer relief from blepharospasm than facial nerve avulsion and has fewer complications. However, it is technically difficult, time consuming, and has greater peroperative morbidity. Facial nerve avulsion may therefore still have a role in selected patients.**

Essential blepharospasm is an idiopathic disorder of progressive involuntary spasms of the orbicularis oculi and upper facial muscles. It may occur in isolation or as part of a spectrum of dystonic movements of other facial, oral, mandibular, or cervical muscles. The condition usually presents in middle age and is more common in women than men.[1] It often begins with episodes of increased blinking of variable duration. This gradually progresses to involuntary spasms of eyelid closure. The course thereafter is very variable, with remissions and exacerbations and in some cases progression to involvement of other muscle groups. Eventually the patients may develop such severe spasms that they become functionally blind and cannot work or care for themselves.[2]

Spasms may be precipitated by certain factors such as reading, driving, stress, or bright light, and they may be alleviated by others such as talking, walking, or relaxation.[2]

A wide variety of treatments have been used in an attempt to alleviate blepharospasm.[1 2] Psychotherapy, hypnosis, acupuncture, faith healing, and herbal remedies have all been tried, with limited success. Several drugs have been reported to ameliorate specific types of blepharospasm,[1] but their efficacy seems to be limited and temporary in most cases.[1] Drugs which have been used include antidepressants, antianxiety agents, anticonvulsants, antiParkinsonian drugs, and muscle relaxants.

Botulinum-A toxin is currently regarded as the best temporary treatment for blepharospasm.[3 4] By interference with acetylcholine release from nerve terminals it results in temporary paralysis of the injected muscles. Subcutaneous injections of botulinum toxin into the upper and lower lid and eyebrow give temporary relief of eyelid spasm and initially have a high degree of patient acceptance. Repeat injections are required initially after three-four months, and then more frequent injections of larger doses may become necessary to control spasms.[5]

Many surgical procedures have been tried to interrupt the pathway from the motor cortex to the orbicularis oculi muscles.[1] Initially they took the form of peripheral facial neurectomy by alcohol injections, surgical sectioning, or percutaneous thermolysis.[6–9] With time the most popular surgical technique became selective peripheral facial nerve avulsion.[10 11]

More recently, however, a direct approach to the muscle has been advocated by stripping of the orbicularis and the brow muscle fibres combined with brow fixation.[12–14] At the present time both selective facial nerve avulsion and orbicularis myectomy are performed at Moorfields Eye Hospital for patients who require surgical treatment.

We have reviewed the management of patients in this hospital with essential blepharospasm over the past 15 years, during which time botulinum toxin has become established as the initial treatment for this condition. We have looked at the long-term success and complications of facial nerve avulsion and compared them with the results from the newer muscle stripping procedure. We have then attempted to draw some conclusions as to the role of each of these procedures in the management of essential blepharospasm.

## Patients and methods

We reviewed the case notes of 56 patients who received surgical treatment for essential blepharospasm between 1975 and 1990 at Moorfields Eye Hospital. Facial nerve avulsion has been performed throughout this period; orbicularis myectomy was first performed in 1983.

The following information was recorded: treatment received prior to surgery, type of surgery, duration of relief from spasms after surgery, complications or secondary effects of surgery, and further treatment necessary after surgery to obtain relief from blepharospasm.

Facial nerve avulsion was performed under general anaesthesia without muscle relaxation.

The facial nerve was approached at the anterior border of the parotid gland. All temporal, zygomatic, and buccal branches were identified by nerve stimulation and avulsed, as were any branches of the mandibular branch which were found to cause contraction of the muscles of the upper face.

Protractor myectomy was performed under general anaesthesia. In the first two cases all four lids were operated on. But because this surgery took more than four hours and involved consider able blood loss subsequent patients had only upper lid surgery in the first instance followed by lower lid surgery at a later stage if blepharospasm was not adequately controlled.

The excision of the upper eyelid orbicularis fibres and brow protractor muscles (corrugator supraciliaris and procerus) was carried out through a brow and eyelid incision. All visible muscle fibres were removed, while the surgeon attempted to preserve the supraorbital nerve. The levator aponeurosis was reinserted and secured to the tarsus to correct any ptosis, and the brows were elevated and fixed to periosteum with a series of non-absorbable sutures.

Even upper lid surgery alone is time consuming, taking up to three hours, and may result in major blood loss. On two occasions it was necessary to defer surgery on the second side until the patient was haemodynamically stable.

## Results

Surgical treatment for essential blepharospasm was performed in 56 patients. As their primary surgical procedure 48 underwent facial nerve avulsion and eight orbicularis stripping. A further three patients then went on to have orbicularis stripping after facial nerve avulsion, making 11 in total.

Of the 48 patients undergoing facial nerve avulsion 28 were female, 20 male, with mean age at surgery of 61·2 years (range 36–83 years). Of these patients 35 had tried medications for their blepharospasm prior to surgery with no long-term success in any case. Fourteen had been controlled for periods of up to 17·5 months with botulinum toxin therapy, and one had had bilateral blepharoplasty previously.

After facial nerve avulsion the mean follow-up was 43·4 months (range 1–154). In 15 of the 48 patients (31%) blepharospasm was controlled to an acceptable level throughout follow-up after one operation. Another six were controlled following reavulsion of residual nerve fibres in the early stages after surgery or of regenerating nerve fibres at a later stage (in total 14 patients underwent repeat facial nerve avulsion, four within four months of the initial procedure and 10 later – mean 14·4 months, range 1–34 months). In 27 (56%) patients blepharospasm was not adequately controlled by one or more facial nerve avulsions during the period of follow-up. Of these, 19 went on to have botulinum toxin therapy, five had medical therapy, and three had the orbicularis stripping procedure.

Twenty (42%) patients required one or more corrective lid procedures following facial nerve avulsion – 16 for ectropion, four for brow ptosis, and two for dermatochalasis. No patients suffered from significant long-term exposure keratitis, though all patients were routinely given tear supplementation in the early postoperative period. Epiphora was a common complaint soon after surgery but settled in the majority of cases, and in no case was lacrimal surgery required. Five patients were troubled by collections of saliva in the parotid gland, and in three cases this necessitated multiple aspirations over a few days until it settled.

Of the 11 patients undergoing the orbicularis stripping procedure nine were female and two male, and their mean age was 64·4 years (range 51–78 years). Prior to surgery seven of the patients had undergone medical therapy. Six had been controlled with botulinum toxin injections for a mean period of 17 months until the injections were no longer effective or were required at too frequent intervals to be practical. Three had troublesome blepharospasm despite previous facial nerve avulsion. After protractor myectomy the mean follow-up was 23·7 months (range 1–80 months).

Eight (72%) of the 11 patients had acceptable control of blepharospasm throughout follow-up after the upper lid orbicularis stripping procedure alone. Three (27%) patients required further treatment for blepharospasm. This consisted of lower lid orbicularis stripping alone in one case, lower lid orbicularis stripping followed by botulinum toxin injections in the second case, and botulinum toxin injections alone in the third case.

After the orbicularis stripping procedure most of the patients had marked postoperative swelling and bruising, but this settled. Only one patient required corrective lid surgery for a lower lid ectropion, which followed lower lid orbicularis stripping. Three patients were treated for minor degrees of corneal exposure but only for a short time after surgery. One patient, who was known to have partial nasolacrimal duct obstruction prior to surgery, now has persistent epiphora thought to be due to the additional effect of reduced function of the orbicularis mediated lacrimal pump and is awaiting dacryocystorhinostomy.

The probability of recurrence of blepharospasm with time after facial nerve avulsion and orbicularis myectomy was plotted after Kaplan-Meier analysis (Fig 1).

## Discussion

At the present time 150 patients with essential blepharospasm are controlled by botulinum toxin injections at Moorfields Eye Hospital. Of these, 32 also require supplemental medical therapy, mostly with benzhexol. The mean follow-up time for these patients is 40 months. Patients who respond poorly to botulinum toxin injections either initially or after repeated injections are candidates for surgical treatment. Since botulinum toxin therapy became widely available in 1985 a total of 20 patients have undergone surgical treatment for blepharospasm after failure of toxin treatment. In the 5-year period prior to this 25 patients underwent surgical treatment. It is our belief that the number of patients requiring surgical treatment for blepharospasm has declined since botulinum toxin became available, but it is too early yet to say what proportion of those patients at present controlled with toxin will ultimately require surgical intervention.

It is very difficult to make an objective comparison of the relative success of different treatments for blepharospasm in terms of actual reduction of spasms.[12,14] However, an important measure is the proportion of patients who require further treatment to control their blepharospasm while under review. After facial nerve avulsion 15 of the 48 (31%) patients required no further treatment and a further six were controlled after a second avulsion procedure. Thus 43·75% in all were controlled with facial nerve surgery alone throughout the study. After orbicularis myectomy eight of the 11 patients were relieved by a single operation (73%) and one other after lower lid stripping, making 81·8% in all controlled by orbicularis muscle surgery throughout the period of review. This is similar to the findings of other series.[13,14] However, since follow-up is much longer in the facial nerve avulsion group, and therefore recurrence more likely, Kaplan-Meier analysis is necessary to provide a more accurate comparison of the two groups (Fig 1). After facial nerve avulsion 50% of patients had recurrence of disabling spasms within 15 months of surgery and only 25% had relief from spasms for more than two years. Other series have quoted recurrence rates of 35–40% at 15 months and 50–55% at two years,[7] but this obviously depends on a highly subjective assessment by the patients.

After orbicularis myectomy relief is more prolonged, with a 50% recurrence rate not observed until almost 30 months after surgery and 55% of patients obtaining relief for more than two years. Myectomy appears to offer the longer relief, but both methods require adjunctive treatment to maintain relief from blepharospasm.

It is important to consider how successful each of these treatments was in combination with adjunctive therapy, medications, or toxin rather than in isolation. It is well known that such therapy is more successful after either facial nerve avulsion or myectomy.[15] All the patients who have required further treatment with botulinum toxin after myectomy have had a good response, and their spasms are well controlled. Following facial nerve avulsion this has also been true with the exception of three (6%) patients whose spasms were not well controlled and so underwent myectomy with good effect.

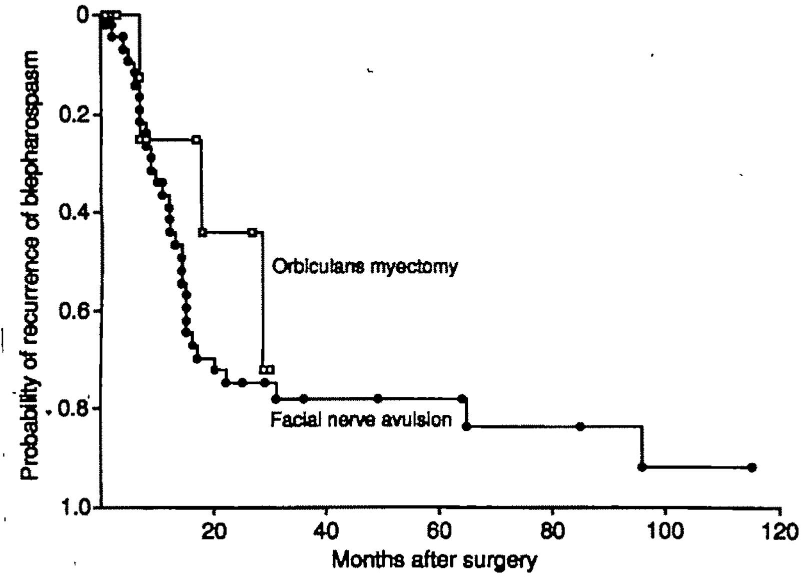

*Figure 1 Kaplan-Meier curve for probability of recurrence of blepharospasm after surgery.*

Secondary effects of facial nerve avulsion that may require surgery include paralytic ectropion, epiphora, lagophthalmos, exacerbation of upper lid dermatochalasis, lip paresis, drooping of the mouth, collection of saliva, and a variable degree of loss of facial expression.[8,13]

A change in facial appearance is inevitable after this form of surgery, with drooping of the brows and of the corners of the mouth. However, after bilateral surgery the appearance of the face is symmetrical and fairly acceptable cosmetically. The loss of facial expression is obviously a serious consequence but one which was considered to be preferable to disabling blepharospasm by all the patients in this series, as has been the case in other series.[11]

Secondary effects of myectomy are reported to be less than those of facial nerve avulsion,[13] and we found this to be the case. Those commonly described include considerable swelling and ecchymosis postoperatively, numbness of the forehead due to supraorbital nerve damage, chronic periorbital lymphoedema, exposure keratitis, and ectropion.

When the complications of the two forms of surgery are compared, myectomy appears to be the safer procedure. Only one of the 11 patients required surgical treatment for complications of myectomy (ectropion repair), whereas 20 of the 48 patients who underwent facial nerve avulsion required further surgical treatment for ectropion, brow or lid ptosis. This is similar to the findings of other series.[8] In neither group did any patient suffer from severe corneal exposure, and though watering of the eyes was a common complaint in both groups only one patient was troubled sufficiently to consider lacrimal surgery.

Both groups of patients were of similar age and sex, and had similar treatment for blepharospasm prior to surgery. The decision as to whether myectomy or facial nerve avulsion was performed depended simply on which consultant they were referred to. In this series myectomy offered more prolonged relief from blepharospasm than facial nerve avulsion. Furthermore myectomy had fewer secondary effects, though no patient in either group suffered from severe corneal exposure or other major complication. The major disadvantage of myectomy is that it is a technically difficult and time consuming procedure, with the possibility of major blood loss.[12,13]

In conclusion, we believe that botulinum toxin is the treatment of first choice in essential blepharospasm. If symptomatic spasms recur, surgery is justified and should not be deferred, as serious complications appear to be rare after either nerve avulsion or myectomy. In otherwise fit and healthy patients myectomy is the surgical treatment of first choice, because of its longer effect and fewer complications. However, facial nerve avulsion may still have a role as a primary procedure in the elderly or infirm because of its lower peroperative morbidity.

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# Fine needle aspiration biopsy in orbital tumours

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**Abstract**

**Fine needle aspiration biopsy (FNAB) was performed in 46 patients with an orbital mass. Positive cytological identification was made in 43 biopsy specimens. In 26 cases with histopathological control the accuracy was 81%. In experienced hands FNAB is safe and appears to be a valuable tool in establishing a diagnosis of malignancy in orbital tumours.**

Fine needle aspiration biopsy (FNAB) has been used in the diagnosis of neoplasms of various organs such as thyroid, pancreas, lung, abdomen, or breast.[1–4] Schyberg[5] was the first to describe its use in orbital tumours. Ideally FNAB should establish the diagnosis of a malignant unresectable orbital neoplasm, to eliminate or plan the need for surgical intervention.

In this study the value of FNAB in the diagnosis of orbital tumours is evaluated, and its place in the management of orbital tumours will be discussed.

## Material and methods

Between 1984 and 1990 FNAB was performed in 46 of the patients referred to the Orbital Centre with an orbital mass. The technique has been described previously in more detail.[6] A 23 gauge needle attached to a 20 ml disposable syringe held in a pistol grip (Cameco, Sweden) is used. After thorough cleaning of the skin the area above the tumour is firmly held with one hand and the needle is inserted through the skin into the lesion. No local anaesthesia is required. When the needle enters the tumour, the operator retracts the plunger, obtaining a negative pressure in the system. To aspirate sufficient material the needle is moved back and forth into the lesion while the vacuum is maintained. Then the plunger is released, equalising the pressure in the system, and the needle is withdrawn from the mass and slides are prepared. The accuracy of the FNABs with histopathological control was calculated.

## Results

The age of the patients at presentation varied from 20 to 89 years (median 60 yr). There were 29 women and 17 men. The presenting symptoms were swelling in 14, ptosis in 12, pain in 11, proptosis in 11, diplopia in 10, visual acuity decrease in three, and epiphora in two patients. The site of the tumours was superotemporal in two, on the eyelid in 15, superonasal in two, retrobulbar in one, and in the lacrimal sac in one. The extent of the tumour was established by computed tomography (CT) in all cases. Biopsy was performed on retrobulbar tumour with CT guidance. The cytological diagnoses are listed in Table 1. Three biopsies yielded insufficient material. Eighteen of the aspirates were diagnosed as benign whereas 25 were diagnosed as malignant. Histopathological control was available in 26 cases (57%). In 21 cases histopathology confirmed the cytological diagnosis. In five cases the cytological diagnosis did not correspond to the histopathology. The cytological diagnosis was pseudolymphoma in these five cases, whereas histopathological control showed a non-Hodgkin's lymphoma in three cases and a liposarcoma in two cases. This yields an accuracy of 81% in the group with histopathological control.

## Discussion

A major area of concern in FNAB is sampling error. While the accuracy is high, false positive reports which may lead to an operation as the result of a faulty diagnosis are almost non-existent. In the group with histopathological control the accuracy was 81%. However, in five cases cytological diagnosis did not show a malignancy whereas histopathological control did, so we still have to regard non-malignant results of an FNAB with suspicion.

In other studies of FNAB of the orbit the accuracy varied from 47 to 100%.[7–12] But not all biopsies had histopathological control. Krohel *et al* found only 47% accuracy in FNAB under direct visualisation.[7] In their study there was a routine pathological examination after surgery in all cases, but 50% of the lesions did not lend themselves to identification by FNAB.

The indication for FNAB in all patients was to establish or exclude a diagnosis of malignancy, which is mandatory in deciding between surgery and observation. In operable cases surgical treatment may be systematically planned at an early stage; in inoperable cases it may suffice to establish the diagnosis.[1] It is a simple and safe diagnostic method[11 13–16] and provides the necessary information with minimal or no alteration in the natural behaviour of the tumour.[18] FNAB is usually less painful than a venepuncture, so there is no need for local anaesthesia. In this way the distortion of the local anatomy can be minimised.[17] Needle tract seeding described after punctures in other places[18–21] was not observed.

*Table Cytological diagnosis after FNAB (n=46)*

| | |
|---|---|
| Pseudolymphoma | 9 (9)* |
| Non-Hodgkin's lymphoma | 8 (2) |
| Adenocarcinoma | 7 (2) |
| Non-specific inflammation | 6 (4) |
| Squamous cell carcinoma | 4 (2) |
| Pleomorphic adenoma | 4 (4) |
| Adencystic carcinoma | 1 (1) |
| Dermoid cyst | 1 (1) |
| Neuroblastoma | 1 |
| Old haematoma | 1 (1) |
| Eosinophilic granuloma | 1 |
| Inadequate specimen | 3 |

*Histopathological control in parentheses

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When the tumour is located in a palpable site, the biopsy is easier than when it is situated deep in the orbit. Kennerdell *et al*[13] advocate that fine needle aspiration should not be used for lesions that are anterior to the orbital septum, but prefer incisional or excisional biopsy techniques for these lesions. We consider FNAB easy and less invasive than an incisional biopsy. Since doubtful non-malignant results can easily be verified, our first choice will be FNAB in these preseptal lesions.

The CT scan is an indispensable tool in locating a process in the orbit.[16] If the mass is inside the muscle cone adjacent to the optic nerve, ultrasound usually provides helpful guidance. Orbital apex tumours and optic nerve lesions may be reached with CT guidance.[13 15–17 22–24] Without the help of CT or ultrasound FNAB should be restricted to preseptal and parabulbar areas to prevent complications.[22]

Better results are obtained when all the aspirations are performed by one clinician who is proficient in the technique.[25] The specimen should be interpreted by one person both familiar with the identification of cells in smears and experienced in orbital pathology. If any of the team members are not available or a lack of enthusiasm for the technique predominates, it is doomed to failure.[13]

Because FNAB acquires a small volume of tissue at the tip of a needle, representative tissue may not be obtained and a sampling error is introduced. One may sample the inflammatory response at the periphery of a neoplasm rather than the neoplasm itself, resulting in a misdiagnosis.[13 26] Wegener's granulomatosis is one of the diseases that can easily be missed owing to its inflammatory appearance.[27] Moreover in tumours of fibrous consistency and those located in the orbital apex, or in lymphocytic lesions, FNAB is less reliable.[28]

Considering the good results that have been reported, together with our own, we consider a FNAB to be reliable if the cytology points in the direction of malignancy. In contrast, a non-malignant cytological diagnosis should not be considered an unequivocal proof of absence of malignant disease. Lesions whose aspirates contain non-diagnostic material and whose clinical appraisals are in disagreement with the cytological findings (in our series the pseudolymphomas) should always be subjected to biopsy for histopathological examination.[29]

In conclusion, FNAB is a rapid and minimally invasive diagnostic technique that shortens time in hospital and reduces the costs of health care.

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# Regression analysis of visual field progression in low tension glaucoma

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**Abstract**

**Eighty four patients (168 eyes) with low tension glaucoma were retrospectively reviewed (mean follow-up was 28 months). The mean age was 66 years, and 69% were females. Regression analysis of their automated Humphrey fields (a mean of eight fields per eye) showed progression in 50% of patients and in 37% of eyes. There was no statistically significant difference between patients with progression and non-progression with respect to age ($p<0\cdot5$) or intraocular pressure ($p<0\cdot5$). Visual field defects were located most frequently in the superior hemifield in both groups of patients. A considerable proportion of patients had advanced field loss at the time of diagnosis.**

Low tension glaucoma (LTG) has always been an intriguing form of optic neuropathy. As early as 1857 von Graefe[1] noted disc cupping and pallor in some eyes in the presence of normal intraocular pressure. Since then the characteristics and details of visual field defects in LTG have been studied[2,3] and frequently matched and compared to those in high pressure glaucoma.[4-8] Despite this there is little evidence of the natural history of field loss in LTG. In earlier studies the number of patients and fields was relatively small. Chumbley and Brubaker[9] reported progression in 41% of 34 eyes (17 patients). Levene[10] found the same proportion in his extensive review of 34 eyes in 23 patients. Anderton *et al*[11] also observed 40% of 56 patients worsening when followed up for a mean of 10·5 years. Glicklich *et al*[12] were the first to use automated perimetry to study progression in LTG. Their figure was 53% at three years and 62% at five years follow-up. All his 36 patients were on medical treatment and 65% had a surgical procedure. His analysis was made on only three fields per eye.

We retrospectively reviewed patients with LTG followed up at Moorfields Eye Hospital. Regression analysis of automated fields was performed to determine the proportion of eyes which showed definite progression.

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## Patients and methods

Patients with LTG followed up in the Glaucoma Unit at Moorfields Eye Hospital were retrospectively looked at for the purpose of our study. Many of these patients were reported on earlier, with manual perimetry studies.[11] The present report includes findings obtained with automated perimetry only.

Our criteria for diagnosing LTG were: (1) a mean intraocular pressure of 21 mm Hg or less; (2) glaucomatous optic disc cupping; (3) glaucomatous nerve fibre field loss; (4) open angle by gonioscopy; (5) absence of other ocular pathology.

Our patients were seen at three-monthly intervals. At each visit a mean of three intraocular pressure readings was obtained with the Goldmann tonometer. The anterior segments and optic discs were assessed by one of three glaucoma specialists and compared with the findings at previous visits. Humphrey automated perimetry using the central 30–2 program was also performed. Stereo optic disc photos were taken yearly. Visual fields were considered for analysis only if reliable. Reliability was defined[12] by (*a*) absence of fixation losses; (*b*) a false positive rate less than 20%; (*c*) a false negative rate less than 20%; (*d*) constant stimulus and pupil size. The criterion of abnormality of fields was the presence of three contiguous points depressed by >5 decibels when compared with age matched normal persons within the central 30°.[12]

All analysed patients met the above criteria with respect to intraocular pressure, visual fields, and optic disc appearance. Patients whose mean intraocular pressure went over 21 mm Hg during the follow-up period were excluded from the analysis. The same was true of those who developed significant lens opacities leading to poor visual testing performance.

Linear regression analysis was done on each tested retinal location in the Humphrey fields of each patient. At and from the third field onwards the sensitivity of each point in decibels was compared with that of the previous field. A slope showing a change in sensitivity of less than 0·2 decibel per month was considered to denote stability. On the other hand a slope showing a decrease in sensitivity of more than 0·2 decibel per month with a correlation coefficient of significance $p<0\cdot05$, was considered to denote progression (that is, worsening) in that specific point.

For the purpose of this analysis progression in a visual field was considered to have occurred if at least the last two consecutive slopes of one or more tested locations were negative ($p<0\cdot05$). All other possibilities, including a single negative regression slope, were considered to indicate a static field.

The location of the visual field defects was also looked at. They were categorised as being paracentral, altitudinal, or occupying a certain quadrant.

## Results

Eighty four patients (168 eyes) met the study criteria. Fifty eight (69%) were females, giving a female to male ratio of 3:2. This is no different

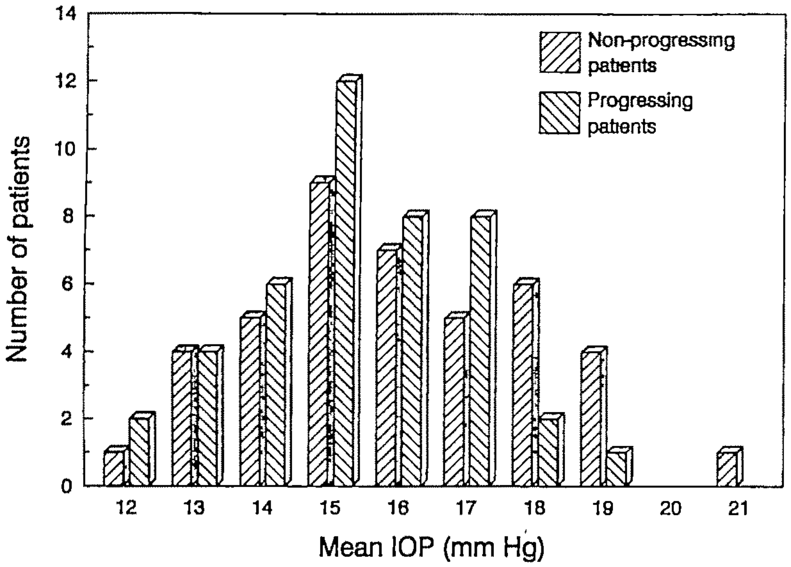


*Figure 1 Distribution of patients according to their intraocular pressure means.*

from that reported in previous series.[7,8,10,12] Their ages ranged from 38 to 86 years, mean 66 years. They all had in-hospital day phasing. Thirteen (17%) of them had phasing repeated – once on presentation to the Glaucoma Unit at least six years before, and a second time more recently. Neurological disease was ruled out in every case. No patient was on any antiglaucoma treatment. A visual acuity of 6/12 or better was present in each eye, and no lens opacities existed at the time of field testing.

The follow-up ranged from eight to 48 months, mean 28 months. Two-thirds of the patients had been attending the LTG clinic for at least six years. The mean number of Humphrey fields per eye was eight, with a range of four to 14. All but 10 patients had bilateral field defects, the rest had unilateral defects. They were included in the study as they satisfied all other criteria. The mean IOP was 16 (15·98) mm HG, range 7 to 26 mm Hg. (A single patient had one reading of 26 mm Hg; his mean intraocular pressure was 15·7 mm Hg over 38 months.) The distribution of patients and eyes according to their IOP means is shown in Figs 1 and 2 respectively. Forty-two (50%) patients and sixty-two (37%) eyes were shown to have progressed. Among those patients who progressed 20 (25%) did so in both eyes, while 22 (26%) progressed in one eye only. Table 1 lists the mean age and mean IOP for patients and eyes.

Statistical analysis by comparison of the means showed that there was no statistically significant difference between progressing and non-progressing patients with respect to age ($p<0{\cdot}5$) or IOP ($p<0{\cdot}5$). The same was true between patients showing progression in one eye and those showing progression in both ($p<0{\cdot}5$). Progressing and non-progressing eyes showed no significant difference in their IOP ($p<0{\cdot}5$). The mean follow-up was 28 months for patients with both progressing and non-progressing eyes.

Table 2 shows the detailed location of the field defects: (*a*) altitudinal (superior and inferior); (*b*) advanced loss (360°); (*c*) paracentral (within 10° of fixation); (*d*) quadrantic (supero- or inferonasal, supero- or inferotemporal); (*e*) vertical (nasal or temporal). Fig 3 shows the same by restricting the analysis to the superior and inferior hemifields and to advanced and paracentral loss.

*Figure 2 Distribution of eyes according to their intraocular pressure means.*

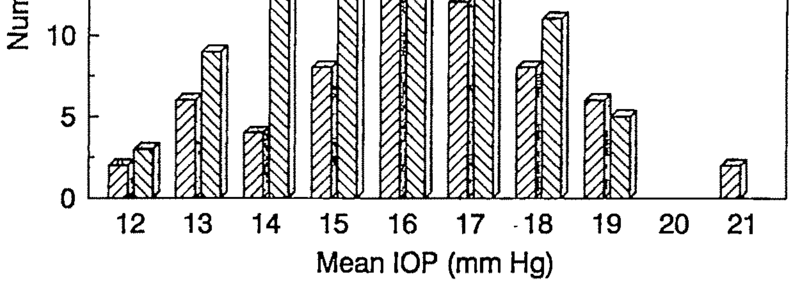


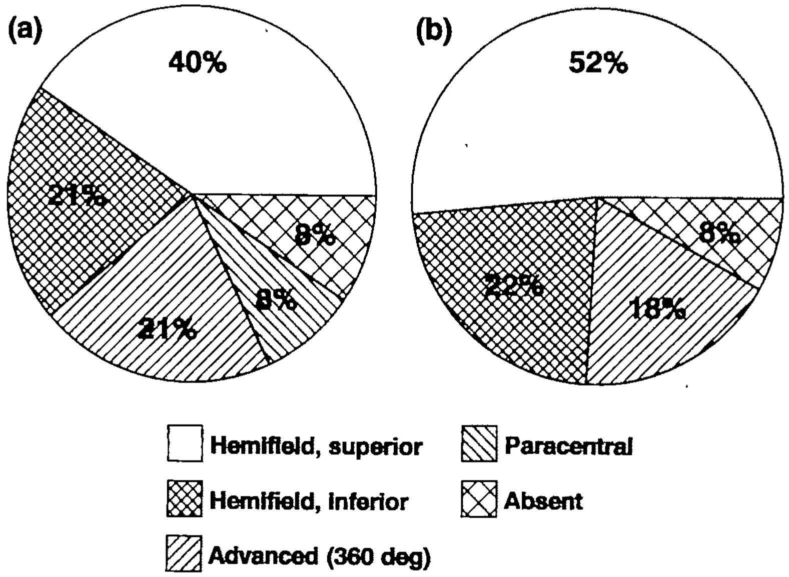
*Table 1 Age and intra-ocular pressure (IOP) expressed as means, standard deviations (SD), and ranges in groups of patients and eyes*

| | | *Age in years* | | *IOP in mm Hg* | |
|---|---|---|---|---|---|
| | *Number (%)* | *Mean (SD)* | *Range* | *Mean (SD)* | *Range* |
| Patients with non-progressing eyes | 42 (50%) | 65 78 (10·03) | 38–86 | 15·60 (1·57) | 07–22 |
| Patients with progressing eyes | 42 (50%) | 66·16 (10·21) | 47–85 | 16·09 (1·98) | 07–26 |
| Patients progressing in one eye | 22 (26%) | 66·63 (9·84) | 47–85 | 15·97 (2·21) | 07–22 |
| Patients progressing in both eyes | 20 (24%) | 65·65 (10·58) | 48–84 | 16·27 (1·99) | 07–26 |
| Non-progressing eyes | 106 (63%) | | | 15·66 (1 73) | 07–24 |
| Progressing eyes | 67 (37%) | | | 16·17 (1 94) | 07–26 |

## Discussion

Linear regression analysis gave negative regression slopes significant at the 0·05 level in 50% of patients (37% of eyes). These figures compare well with these reported by Chumbley and Brubaker,[9] Levene,[10] and Anderton *et al*[11] using manual perimetry. They are lower than the 53% and 62% reported by Glicklich *et al*[12] at three and five years of follow-up respectively with computer assisted perimetry. One reason for the difference between our results and those of Glicklich *et al* is that we included as 'progression' only those eyes with evidence of continued progression on repeat testing three to six months later.

Compared with cases of high pressure glaucoma, cases of LTG scotoma were found to be closer to fixation,[2,4,6,10] and to be deeper and to have steeper slopes by some authors[2,4] but not by others.[6] However, all published material agrees that the superior hemifield[3,4,11] and specifically the superonasal quadrant[12] are the most frequent locations for LTG defects. Our analysis (Table 2) also shows the superior hemifield to be mostly affected in both non-progressing and progressing eyes (40% and 52% respectively). Advanced loss (360°) was found in 21% and 18% respectively. This comes as no surprise. Being asymptomatic in terms of IOP, LTG patients are discovered late in the course of their disease. A number of eyes (4% of non-progressing and 13%



*[illegible]igure 3 Location of field [illegible]cts in (a) non-progressing and (b) progressing eyes.*

of the progressing ones – Table 2), have been found to have defects respecting the vertical axis or meridian. This has not been observed before, and it might be partly due to the grouping of test locations by the Humphrey field analyser.

Having confirmed that a high proportion of eyes with low tension glaucoma worsen over comparatively short periods of time, the question arises, what can be done about it? At the present time the favoured approach is to try to delay progression by lowering the IOP. The most published method for this is by fistulising surgery.

Surgery in the management of LTG is well known. Among others, Bloomfield[13] and then Levene[10] realised that progression maintained its same pace despite successful surgery. Hitchings[14] commented on the difficulty of maintaining a significantly low pressure in these patients. de Jong *et al*[15] reported reducing the number of eyes with continued progression to only 8% following a 20% reduction in IOP in 26 eyes of 20 patients with a follow-up of three years.

It should be noted, however, that the patients of de Jong *et al*[15] had a mean preoperative IOP of 22 mm Hg. In contrast, the mean IOP for the patients in this series was only 16 mm Hg, making the task of IOP lowering that much harder. Another problem which occurs in the assessment of the efficacy of IOP lowering as an agent of halting visual loss is the suggested episodic nature of progression. In their long term follow-up of patients with low tension glaucoma Anderton *et al*[11] noted this episodic progression occurring, and that the mean interval between periods of progression was 4·4 years.

*Table 2 Detailed location of field defects in non-progressing and progressing eyes*

| | *Non-progressing eyes* | | *Progressing eyes* | |
|---|---|---|---|---|
| *Location of defect* | *No.* | *(%)* | *No* | *(%)* |
| Altitudinal | | | | |
| Superior | 18 | (17%) | 13 | (21%) |
| Inferior | 4 | (4%) | 5 | (8%) |
| Advanced (360° loss) | 22 | (21%) | 11 | (18%) |
| Paracentral | 9 | (8%) | 5 | (8%) |
| Quadrantic | | | | |
| Superonasal | 22 | (21%) | 13 | (21%) |
| Inferonasal | 12 | (11%) | 3 | (5%) |
| Superotemporal | 1 | (1%) | 2 | (3%) |
| Inferotemporal | 4 | (4%) | 2 | (3%) |
| Vertical | | | | |
| Nasal | 1 | (1%) | 2 | (3%) |
| Temporal | 3 | (3%) | 6 | (10%) |
| Absent defect | 10 | (9%) | 0 | (0%) |

In the absence of any tested alternative for the treatment of low tension glaucoma it is important to assess the hyopthesis that progressive visual loss in this disease occurs because the IOP is too high for the eye and to run a trial of treatment versus no treatment. Such studies are now under way.

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# Self-inflicted eye injuries

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## Abstract

**Five cases of self-inflicted eye injury are described and discussed. A review of the literature shows that several psychiatric diagnoses have been assigned to people who damage their eyes. A variety of mechanisms to explain this phenomenon are described.**

Self-inflicted eye injuries are rare but are referred to in many ancient texts.[1 2]

Oedipism (as distinct from the oedipus complex) is defined as 'self-inflicted injury to the eye,' though some authors restrict it to cases of self-enucleation alone. According to legend Oedipus killed his father, King Laius of Thebes, and married his mother, Jocasta, unaware of the identity of either. Pestilence descended on Thebes, and Oedipus consulted an oracle, who told him that his incest and the murder of his father were the cause of pestilence. In horror Oedipus tore out his eyes and became a blind, wandering beggar. In Norse mythology[2] Odin exchanged one of his eyes for the right to drink a single draught from the spring of Mimir, which offered wisdom and understanding.

Legend has it that Saint Lucia, a pious Sicilian girl (patron saint of eyes), looked lustfully on a nobleman who wished to marry her for the beauty of her eyes. In remorse for her sinful thoughts she tore them out and gave them to him saying, 'Now let me live to my God.' God in His permissive wisdom gave her two new eyes. She is represented in art carrying a palm branch and a platter with two eyes on it. St Triduna and St Medana, patron saints of ophthalmology, also blinded themselves in remorse for sinful thoughts but were not rewarded with new eyes by God. In the 13th century Marco Polo, on reaching Baghdad, was told the story of a cobbler who destroyed his right eye with his awl after he had sinful thoughts when the leg of a young woman was exposed as he fitted her with slippers.[3] The notion of self-blinding for sinful thoughts also occurs in the Bible[4]: 'Everyone who looks at a woman lustfully has already committed adultery with her in his heart. If your right eye causes you to sin pluck it out and throw it away; it is better that you lose one of your members than that your whole body be thrown into hell.'

Psychiatric and other medical reports of self-enucleation and blinding are rare and date back to 1846 when a case of self-blinding was described by Bergman as 'delire mystique.'[5] In his review of the literature from 1846 to 1968 Gerhard[5] found only 10 cases of self-enucleation.

A variety of functional and organic psychiatric disorders have been reported in cases of self-enucleation. Schizophrenic psychoses,[6] psychotic depression, epilepsy,[7] lysergic acid diethylamide psychosis,[8] encephalitis,[9] Lesch-Nyhan syndrome,[10] Gilles de la Tourette syndrome,[11] and diabetes mellitus with renal and vascular involvement.[12]

Self-inflicted traumatic cataracts, detached retinas, and lens dislocations have been described in a case of obsessive compulsive neurosis in which a man repeatedly hit his eyes with his hands.[13 14]

## Case reports

### CASE 1

A 29-year-old single man with no past psychiatric history was admitted to hospital following se[illegible] self-inflicted lacerations to his neck. On his way to the operating theatre for repair of the lacerations he attempted to blind himself in both eyes by inserting the index fingers of both hands between his eyes and the bridge of his nose (as described by Axenfeld[15]) in order to tear his eyes out.

He damaged both eyes so severely that the left eye had to be surgically enucleated shortly after the laceration to his neck had been repaired. Histological examination of the left eye revealed a collapsed eye ball measuring 2·1×2·1×2·1 cm, with adherent blood clot from the scleral surface. A perforation 1·2 cm in diameter was present at the vertex of the eye, with a further perforation 0·8 cm in diameter anterior to this in the sclera. This was 0·7 cm from the corneal edge. The lens and iris were intact, but the posterior chamber was full of blood.

Microscopically the anterior chamber was intact, the cornea, iris, and lens showing no significant abnormality. The posterior chamber was severely disrupted, however, with haemorrhage into the subretinal space and resulting detachment of the retina. Vitreous humour was not identified. There was a perforation of the sclera, noted macroscopically, and an early acute inflammatory reaction in the anterior episclera.

The appearances were consistent with traumatic rupture and avulsion.

The right eye also had a severe perforating injury resulting in a circumferential scleral rupture of more than 180° inferiorly with dislocation of the lens. There was massive vitreous incarceration requiring a combined vitrectomy, 360° relieving retinal incision, and endolaser. There was no encirclement. Silicone oil was injected into the vitreous cavity. Endolaser was performed. There was a patch of epiretinal membrane over the macula which was successfully dealt with by membrane peel. His retina has remained attached for a period of three months after surgery. Despite these repairs his vision at the time of this report is very poor, he can only count fingers and distinguish light from dark. There is considerable macular puckering, and it is doubtful if there can be much further improvement.

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He later explained that an auditory hallucination had commanded him to kill himself because he had cancer. He attempted to remove his eyes because the voices had told him that anyone he looked upon would be cast into hell. He is at present receiving neuroleptic medication and has not attempted to harm himself again.

### CASE 2

A 41-year-old single man was admitted to a psychiatric unit suffering from a schizoaffective psychosis complaining of auditory hallucinations and feelings of worthlessness. After admission he attempted bilateral enucleation of his eyes using the fingers of both hands. He was transferred to an ophthalmology ward, but his sight could not be restored.

He responded well to neuroleptic medication and electroconvulsive treatment (ECT), later admitting that 'the voices told me to take my eyes out.' He was readmitted three months after discharge with further auditory hallucinations and the delusion that he had venereal disease, and he attempted to castrate himself on the ward. Again he responded well to ECT and neuroleptics and remained well for 10 years until his third admission 11 years ago complaining of auditory hallucinations ordering him to tear his eyes out. For the past 11 years he has remained free of symptoms on depot neuroleptic medication.

### CASE 3

A 16-year-old male was admitted to a psychiatric unit from a casualty department with a severe self-inflicted orbital apex injury to the left eye with a metal pipe, which resulted in blindness and ophthalmoplegia to the left eye. Six weeks before admission his parents noticed he had become increasingly withdrawn. They were woken one morning by noise in the kitchen, where they found the patient thrusting a cold water pipe he had torn from under the sink into his eye. After admission to hospital he made repeated attempts to tear out his eye and jump from the first floor window. An organic cause for his disturbed behaviour was excluded and screening for drugs gave negative results. He responded to neuroleptic medication and claimed that he used the metal pipe to get an ant out of his head which he was convinced was present. The tactile hallucination disappeared after he started on neuroleptic medication. He has, however, required depot neuroleptic medication for his chronic schizophrenia.

### CASE 4

A 73-year-old woman admitted to hospital in 1941 with grandiose delusions that she was the Duke of Windsor has for the past 49 years repeatedly punched her left eye and face shouting, 'get away you devils.' This resulted in total blindness to her left eye due to lens dislocation and retrobulbar haematomas. She admits that she hits her eye in an attempt to 'get the voices out of my head' – not in response to the auditory hallucinations. She is receiving neuroleptic medication.

### CASE 5

A 68-year-old woman admitted to hospital in 1940 who had a leucotomy in 1955 has so repeatedly punched the right side of her face in an attempt to rid herself of her distressing auditory hallucinations that she is now blind in the right eye, the result of a lens dislocation and retrobulbar haematomas, and has a cauliflower ear and deformed right thumb. She is receiving neuroleptic medication.

## Discussion

It has been postulated that self-enucleation and other forms of ocular mutilation are symbolic forms of castration.[16] Freud,[17] in his studies of dream fantasies and myths considered that anxieties about sight, fear of going blind, were a substitute for the fear of being castrated. Rosen and Hoffman[8] suggested that sinful sexual transgressions which conflicted with the 'tyrannical' superego could be appeased only by the sacrifice of the offending part (genitals) or its symbolic substitute. For women the eye substitutes for the absent 'disposable' genitals. Meninger[16] considered the proposition that the eye may in fact represent the symbolic condensation of the whole self. Self-enucleation (in keeping with Matthew, chapter 5 verses 28, 29) would represent a 'focal suicide,' in Meninger's term, allowing one to kill the devilish self and yet live.

Trevor-Roper[18] described the eye as the 'sounding-board of the travails of the whole persona' and also emphasised the role of the eye in sexuality. The eye was 'a whipping boy for the wrought psyche.' The eye was a sort of 'sexual surrogate, a convenient organ of displacement whenever fear, guilt, impotence or despair debarred a more physiological outlet.'

Maclean and Robertson,[19] in their review of the literature, found that most reported cases of self-enucleation were 'psychotic' at the time of the act. Yet very few patients with psychosis mutilate their eyes. Those who do appear to have a number of common life events. Loss of a father at an early age, a dominant intrusive mother for whom they have unresolved oedipal conflicts, castration fears, and sexual guilt. These factors together with perhaps a concrete interpretation of the verses in Matthew and an alteration of body image combine and result in the horrendous act of self-enucleation.

The cases we have described support previous authors' findings but highlight one case where self-enucleation was a response to a tactile hallucination and two cases where self-inflicted blinding resulted from patients' vain attempts to rid themselves of their distressing auditory hallucinations.

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## CASE REPORTS

# Transpalpebral extrusion of a silicone sponge exoplant

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### Abstract

**We report an unusual case of scleral buckle extrusion in a 63-year-old woman. A 5 mm silicone sponge exoplant eroded through Tenon's capsule, conjunctiva, and full-thickness upper eyelid, traversing the tarsal plate.**

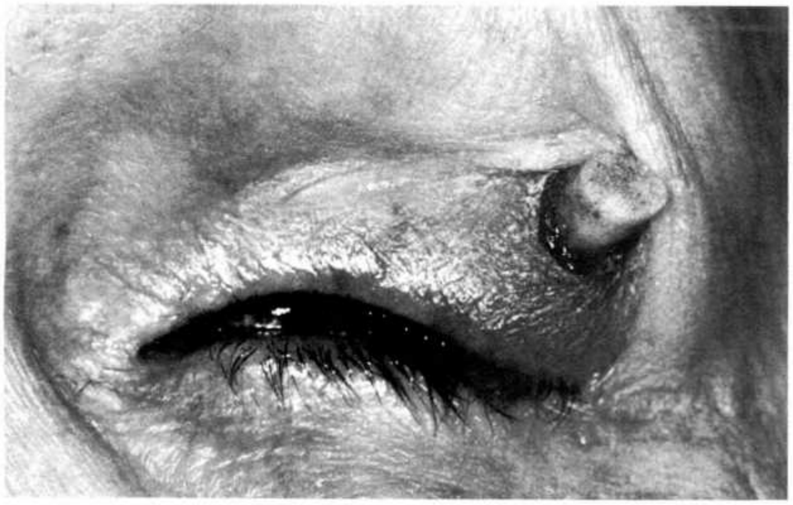

*Figure 1 External photograph showing 5 mm silicone sponge exoplant protruding through the left upper eyelid.*

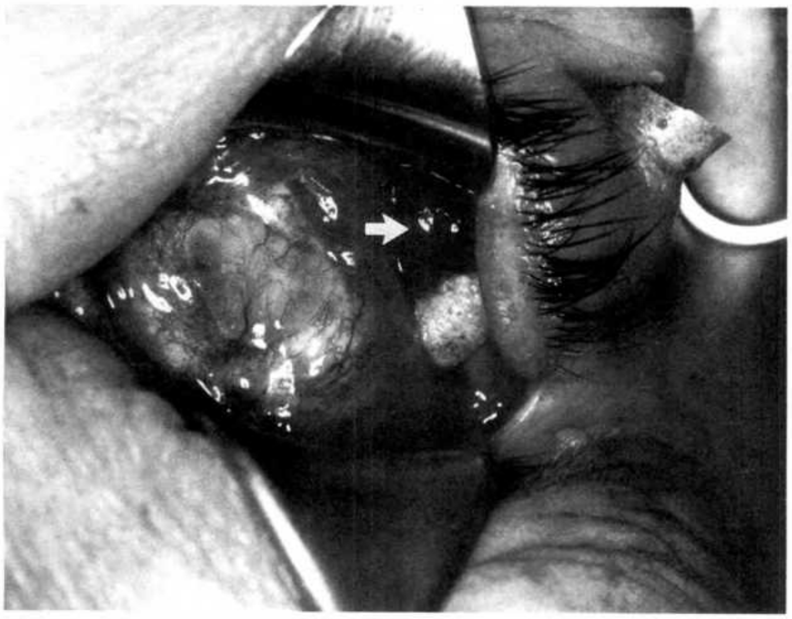

*Figure 2 Phthisical globe with silicone sponge exoplant extruding through conjunctiva and full-thickness eyelid. A large haemorrhagic pyogenic granuloma (arrow) is adjacent to the sponge.*

Extrusion of scleral buckling material is not an uncommon complication of scleral buckling surgery. We recently treated a woman with transpalpebral migration of a soft silicone sponge exoplant, a distinctly unusual presentation of scleral buckle extrusion.

### Case report

A 63-year-old blind woman presented with a one-week history of mild pain and foreign body sensation in the left eye. She had no light perception in the right eye owing to trauma and failed glaucoma surgery many years previously. The left eye had undergone multiple procedures for glaucoma, two penetrating keratoplasties, a scleral buckling procedure, and two subsequent revisions of the scleral buckle combined with pars plana vitrectomy. During the most recent buckling procedure in 1982 the eye was encircled with a 5 mm diameter silicone sponge exoplant. The left eye lost light perception in 1985 owing to recurrent retinal detachment with proliferative vitreoretinopathy.

On examination in July 1990 the left eye was phthisical. The 5 mm silicone sponge had extruded through Tenon's capsule and conjunctiva inferotemporally, and had eroded through full-thickness upper eyelid, including the tarsal plate (Figs 1 and 2). A large pyogenic granuloma protruded from the adjacent tarsal conjunctival surface of the upper lid. The exoplant was removed and the lid defect primarily closed after excising the pyogenic granuloma and the epithelialised tract through skin and orbicularis muscle.

### Discussion

Extrusion and intrusion of scleral buckling elements are well recognised complications of retinal detachment surgery. Intrusion by encircling polyethylene tubes or Arruga sutures was particularly common.[1] It is less common with the newer, softer, more elastic silicone rubber materials.[2] Nevertheless, in addition to transconjunctival erosion, silicone elements have eroded through sclera,[3] into the vitreous cavity,[4] and anteriorly into cornea.[5]

Our patient is unusual in that the extrusion process did not come to medical attention until the silicone sponge had eroded through the tarsus and orbicularis muscle of the upper lid and emerged through the skin surface. For such transpalpebral migration to occur it would be necessary for the eyelid to remain relatively stationary over the extruding exoplant. This patient's bilateral blindness and phthisical left eye almost certainly facilitated the severe extrusion by reducing lid movement as well as patient awareness. We consider that transpalpebral erosion will continue to be a most uncommon presentation of scleral buckle extrusion.

This work was supported in part by the Heed Ophthalmic Foundation (Dr Winward) and the Heed Foundation/Knapp Fellowship (Dr Johnson).

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## FIFTY YEARS AGO

**Superficial epidemic punctate keratitis**

In conclusion it might be useful to add that the designation 'superficial punctate keratitis' or 'keratitis diversiformis et uveitis anterior' would appear to be inappropriate as these do not define the primary condition, but serve to indicate its complication only. Our experience would seem to show that it is primarily a disease of the conjunctiva caused by an exogenous infection which according to its severity spreads to the lymphatic glands in one direction, and, in the other direction, to the adjacent tissues of the conjunctiva, involving the cornea and uvea, causing superficial or deep complications according to the depth to which the infection has travelled.

'"Acute kerato-conjunctivitis of undefined origin" occasionally becoming epidemic' would seem more aptly to describe this clinical condition. – Conclusion of an article by Viswalingham A. Epidemic superficial punctate keratitis in Malaya.
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# Nd-YAG laser hyaloidotomy for malignant glaucoma following one-piece 7 mm intraocular lens implantation

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## Abstract

**Three cases of malignant glaucoma following extracapsular cataract extraction with 7 mm one-piece posterior chamber intraocular lens implantation are presented. Nd-YAG laser hyaloidotomy was successfully performed in all eyes, but was difficult and required several sessions in two eyes. In the third eye, which had a sector iridectomy, laser hyaloidotomy applied over the edge of the lens optic through the iridectomy resulted in brisk deepening of the anterior chamber and reduction of intraocular pressure. We propose that the one-piece 7 mm optic posterior chamber intraocular lens may constitute an obstacle to successful hyaloidotomy, mainly owing to its large size, as it may block aqueous percolation from the vitreous into the anterior chamber. Eyes prone to develop malignant glaucoma after surgery should have a sector or large peripheral iridectomy to facilitate postoperative Nd-YAG laser hyaloidotomy if required.**

The application of the Q-switched Nd-YAG laser for aphakic or pseudophakic malignant glaucoma has already been accepted as the surgical treatment of choice in cases where topical treatment with cycloplegic drops has failed. The treatment, as proposed by Epstein *et al*,[1-3] consists in cutting with the laser through the anterior hyaloid face (hyaloidotomy), with consequent release of aqueous trapped in the vitreous gel. This procedure is very effective in relieving the 'vitreal block', and aqueous diversion is reversed in both aphakic and pseudophakic eyes.[4-9]

In recent years the one piece 7 mm optic posterior chamber intraocular lens (PC-IOL) has become popular. This transition to 7 mm lenses was based on the belief that a larger lens would provide better optical centration, less glare, and fewer optical aberrations.

In this study we report on three cases in which malignant pseudophakic glaucoma followed the insertion of 7 mm one-piece IOLs. In two eyes, Nd-YAG laser hyaloidotomy was technically difficult, and the relief of the condition was slow. In the third case hyaloidotomy was easily and successfully done through a pre-prepared sector iridectomy. Possible reasons for such difficulties and some suggestions for minimising them will be discussed.

## Case reports

In the last two years we have detected three eyes that developed malignant glaucoma following extracapsular cataract extraction and insertion of a one-piece 7 mm posterior chamber intraocular lens (IOL).

### CASE 1

A 75-year-old woman underwent uneventful extracapsular cataract extraction in the right eye with insertion of a one-piece 7 mm posterior chamber IOL. She was known to have suffered from chronic angle closure glaucoma in both eyes, and five years earlier bilateral laser iridotomies had been performed. Since then the intraocular pressure (IOP) had been controlled with drops of timolol 0·5% twice a day and pilocarpine 4% four times a day. Prior to surgery the visual acuity of the right eye was counting fingers at 3 feet (1 m), and there was a dense nuclear sclerosis and a moderate diffuse posterior subcapsular cataract. On the first postoperative day the anterior chamber was very shallow, the IOP was raised to 38 mm Hg, and the cornea was diffusely oedematous. Repeated applications of cycloplegic drops were unsuccessful in relieving the condition. Maximal antiglaucoma therapy, which included 0·5% timolol twice a day, 4% pilocarpine, four times a day, acetazolamide tablets 250 mg four times a day, and two doses of hyperosmotic agents (glycerol) were also ineffective. A diagnosis of malignant glaucoma was made, and Nd-YAG laser hyaloidotomy was performed after the cornea had been cleared with the application of glycerin drops. Completely successful hyaloidotomy required four sessions of laser treatment. The laser parameters at each session were: 15–22 pulses of 3–4·2 mJ each delivered through the pupil and the patent laser iridotomy. The aim of the laser treatment was to perforate the hyaloid membrane and allow aqueous, believed to be trapped in the vitreous, to flow into the anterior chamber. After the first three sessions the response was only temporary, with anterior chamber deepening and IOP reduction which lasted no more than 24 hours. Immediately after the fourth laser session the anterior chamber deepened and the IOP dropped to 10 mm Hg and persistently remained in the low teens. After 12 months of follow-up the IOP was 12 mm Hg with timolol 0·5% twice a day only, and best corrected visual acuity was 20/40.

### CASE 2

A 68-year-old man underwent uneventful extracapsular cataract extraction with implantation of a one-piece 7 mm IOL in the right eye. He was known to be hyperoptic in both eyes, with a visual acuity of 20/200 in the right

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and 20/50 in the left eye, best corrected with a + 3·0 sphere and +2·25 sphere respectively. Three years prior to cataract surgery laser iridotomies had been successfully performed, based on a gonioscopical diagnosis of narrow, closeable angles with IOPs of 20 mm Hg in the right and 21 mm Hg in the left eye.

Two days after surgery the IOP was 52 mm Hg in the right eye, the cornea was diffusely oedematous, and the anterior chamber was extremely shallow (less than one corneal thickness measured axially). The optic nerve head and the posterior pole appeared normal. Cycloplegic drops were applied at 10-minute intervals for one hour, with some deepening of the anterior chamber and reduction of the IOP to 40 mm Hg. Antiglaucoma medications were added, including 0·5% timolol twice a day, tablets of 50 mg neptazane three times a day, and two doses of an oral hyperosmotic agent (glycerol). As the IOP remained at 42 mm Hg the following day, Nd-YAG hyaloidotomy was performed through the pupil. Three treatment sessions were required to achieve a persistent functioning hyaloidotomy, with deepening of the anterior chamber and reduction of IOP to 14 mm Hg. The total number of laser applications was 41 pulses of 3·5–4·1 mJ each. After 15 months of follow-up the visual acuity was 20/30, the IOP was 16 mm Hg without medications, the cornea was clear, and the anterior chamber deep.

### CASE 3

A 62-year-old man underwent uneventful extracapsular cataract extraction and 7 mm one-piece IOL implantation in the left eye. Sixteen years previously a superior sector iridectomy had been performed in this eye after an acute attack of angle closure glaucoma. A successful laser iridotomy was later done in the right eye, and the IOP was kept around 18–20 mm Hg without medical treatment and 22–23 mm Hg in the left eye with pilocarpine 2% four times a day. Prior to cataract surgery the visual acuity was 20/400 in the left eye, there were posterior synechiae, and a dense nuclear and anterior cortical cataract. Ophthalmoscopy revealed temporal pallor of the optic nerve head.

Immediately after surgery the anterior chamber was moderate (two corneal thicknesses measured axially), and the IOP was 17 mm Hg. Cycloplegic drops and steroid drops were started four times a day, with some deepening of the anterior chamber. Next day anterior chamber flattening was noted, with IOP elevation to 36 mm Hg. The superior edge of the lens optic was found to be tilted anteriorly with contact to the cornea, and there was adjacent localised stromal oedema of the cornea.

Nd-YAG laser hyaloidotomy was promptly done in the left eye, requiring only 12 pulses of 3·0 mJ each to achieve immediate relief. Treatment that was aimed at the hyaloid behind the lens was ineffective, while laser shots at the hyaloid over the edge of the optic and through the sector iridectomy resulted in immediate deepening of the anterior chamber, with subsequent reduction of the IOP to 10 mm Hg. After 10 months of follow-up the best corrected visual acuity was 20/50, the IOP was 14 mm Hg with pilocarpine 2% four times a day, the anterior chamber was deep, and the IOL was centrally located with no corneal touch.

## Discussion

Total obliteration of the posterior chamber by vitreous and a highly resistant hyaloid membrane have been suggested as a mechanism in aphakic or pseudophakic malignant glaucoma.[6 10] According to this concept, aqueous is diverted into the vitreous cavity, accumulates there, and pushes the anterior vitreous and hyaloid forward, shallowing the anterior chamber.

Epstein *et al*,[11] in experimental perfusion studies of normal, enucleated human and calf eyes, have provided support for Grant's speculation that in malignant glaucoma there may be a decrease in the permeability of the vitreous body or of the anterior hyaloid membrane to the anterior flow of aqueous humour, resulting in increased pressure in the space behind a posteriorly detached vitreous and a decrease in fluid movement through the vitreous gel. Therefore it is presumed that such eyes have a hyaloid membrane which is less permeable to aqueous. As the main pathology lies at the hyaloid and anterior vitreous level, laser iridotomy is usually insufficient to produce communication between the anterior chamber and the trapped intravitreal aqueous. Epstein *et al*[1-3] recommended the use of the Nd-YAG laser for hyaloidotomy in three cases, and successful results reported by others have made this procedure the treatment of choice for aphakic or pseudophakic malignant glaucoma.[1-3 9]

In this study we report on three eyes with pseudophakic malignant glaucoma in which Nd-YAG laser hyaloidotomy was performed but was very difficult and required several sessions in two of the eyes. We believe these difficulties are associated with the 7 mm one-piece PC-IOL. As the optic of this lens is larger and there are only two positional holes (compared with four holes in the 6 mm PC-IOLs), it is harder to aim at the hyaloid membrane and achieve a perforation. In addition, the 'spring-like' effect of the IOL may be greater in these lenses. Unlike the three-piece IOLs, which consist of prolene haptics with much elasticity, the relatively stiff plastic haptics of the one-piece lenses may provide more tension directed anteroposteriorly once implanted in the bag. This characteristic of the one-piece lens may result in more pressure against the hyaloid, with less room for trapped aqueous to pass through into the anterior chamber.

As most of the difficulties related to Nd-YAG laser hyaloidotomy in cases of one-piece 7 mm IOLs result from the size of the optic, we suggest that, when possible, laser treatment should be aimed at the hyaloid beyond the edges of the optic. This can be achieved best through a large peripheral or sector iridectomy, as was shown in the third reported case. We propose that in cases prone to develop malignant glaucoma (especially chronic angle closure glaucoma, hyperopia, or a fellow eye with a history of malignant glaucoma) such iridectomies should be performed during surgery, as is the acceptable practice in cases of anterior chamber IOL implantation. Hyaloidotomy beyond the edge of the optic is easier, as the target is visualised properly; and, once the membrane is successfully cut, aqueous can freely percolate into the anterior chamber and deepen it. Moreover, placing the positional hole of the lens superiorly may result in a better view of the hyaloid through an iridectomy or even after pupillary dilatation.

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# Perforation of the globe – a complication of peribulbar anaesthesia

J P Joseph, J D A McHugh, W A Franks, A H Chignell

**Abstract**

**Peribulbar anaesthesia has been recommended as a safer alternative to retrobulbar anaesthesia. We report a case of perforation of the globe sustained during peribulbar anaesthesia which resulted in blindness. Orbital injections are potentially dangerous, be they peribulbar or retrobulbar. To minimise the risk, short, blunt needles are advocated for the peribulbar route.**

Peribulbar anaesthesia has been advocated as a safer alternative to retrobulbar anaesthesia.[1][2] With the injection of local anaesthetic placed outside the muscle cone there should be no risk of damage to the optic nerve and a decreased risk of perforation of the globe.[3] We report a perforation of the globe sustained during peribulbar anaesthesia which resulted in blindness.

## Case report

An 86-year-old myopic woman of $-8 \cdot 5$ D with an axial length of 25·7 mm, underwent right cataract extraction on a day case basis. Eight years previously she had undergone a left cataract extraction and attained 6/12 vision. Anaesthesia was administered by a standard peribulbar technique. A 2·5 ml injection of a 50/50 mixture of bupivacaine hydrochloride (Marcain) 0·5% and lignocaine 2% was placed both superonasally and inferotemporally in the right orbit via a blunt, disposable Atkinson 25 g retrobulbar needle 3·7 cm length, which was introduced approximately 2 cm below the skin. No preoperative complications were noted, and extracapsular cataract extraction with implantation of a posterior chamber intraocular lens was performed uneventfully.

The patient reported floaters one day after the operation, but these resolved by day 5, at which time her visual acuity was 6/18 with a pin hole. At 13 days she reattended with a one-day history of sudden visual loss in the operated eye. The anterior segment showed a normal postoperative appearance, with posterior chamber intraocular lens. The posterior segment showed an incomplete posterior vitreous detachment and a total retinal detachment with an area of retinal incarceration in the equatorial region of the superonasal quadrant. No peripheral breaks were identified. There was a small amount of vitreous haemorrhage inferiorly.

A pars plana vitrectomy was performed under general anesthesia. An internal search revealed two adjacent ovoid retinal breaks at the site of retinal incarceration, suggesting the entry and exit wounds of the retrobulbar needle. Subretinal fluid was drained internally via the breaks, which were treated with cryopexy and supported by a radial explant. A 30% $SF_6$/air mixture was introduced into the vitreous cavity. On the day after operation day she was noted to have suffered a haemorrhagic choroidal detachment, which spread into the vitreous cavity. One month after operation the haemorrhage had substantially cleared and the retina was seen to be flat, with the retinal breaks closed on the indent. Nine days later, however, her vision deteriorated markedly, with a recurrent total retinal detachment and extensive proliferative vitreoretinopathy. Further surgery was not undertaken.

## Discussion

The case described is unusual in that perforation of the globe was not recognised peroperatively during the cataract extraction. While globe penetration has been previously reported in a case of peribulbar anaesthesia, this was recognised immediately owing to the presence of vitreous haemorrhage.[4] Early vitrectomy was undertaken and vision was preserved at 6/12. The occult nature of the case described and the consequent delay in vitrectomy contributed to the poor outcome.

Perforation of the globe is a well recognised though rare complication of retrobulbar anaesthesia. It is likely to be more common in larger myopic eyes. In a series of 4000 cases of retinal detachment undergoing surgery under retrobulbar anaesthesia the three globe perforations encountered were, as in our case, in highly myopic eyes.[5] Blunt needles have been recommended to decrease the chance of globe perforation when performing both retrobulbar[6] and peribulbar anaesthesia.[7] In our case a blunt tipped needle was used, but globe penetration still occurred. Davis and Mandel, who first described the technique of peribulbar anaesthesia, recommend a needle of 1·9 to 2·2 cm in length, and in a series of over 3000 cases of peribulbar anaesthesia there were no complications.[8] The needle used in our case was 3·7 cm in length. Although the operating surgeon considered that it had been introduced 2 cm below the surface, the situation of the globe perforation suggested that it may have been deeper. Davis and Mandel[8] also recommend a single inferotemporal peribulbar injection, which they find adequate in over 80% of their cases. They found that a superonasal injection was necessary only if inadequate akinesia was achieved with the inferotemporal injection. Presumably limiting the number of injections will decrease the risk of globe perforation. Nevertheless Loots and Venter[9] have reported a series of 400 cases of

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peribulbar anaesthesia without serious complication, using both a 4 cm retrobulbar needle introduced to its full depth and employing two injections per patient.

This case demonstrates that peribulbar anaesthesia may be dangerous. It seems from the site of the perforation that the length of the needle used (3·7 cm) may have increased the risk of this occurence. It seems prudent to heed the advice of Davis and Mandel to use short, blunt needles when employing peribulbar anaesthesia, and to give a single injection where possible. Indeed, the necessity for an orbital injection should perhaps be reconsidered when performing cataract extractions, as subconjunctival infiltration alone with local anaesthetic agents has been shown to provide satisfactory anaesthesia,[10 11] with no greater incidence of complication than with retrobulbar anaesthesia.[10] Using the subconjunctival route alone should virtually remove the risk of globe perforation and the other well known serious, albeit rare, complications of orbital anaesthesia.

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# Eyelid leishmaniasis in a patient with neurogenic ptosis

D P O'Neill, J Deutsch, A J Carmichael, R Taylor

## Abstract

**A patient with chronic progressive external ophthalmoplegia contracted cutaneous leishmaniasis of the upper eyelid. Infection of this site is rare because eyelid movements usually prevent the sandfly vector from biting the skin there. It is postulated that the relative immobility of the upper eyelid in this patient was a major predisposing factor for the infection.**

Leishmaniasis is a protozoan zoonosis transmitted to man by sandfly vectors. The vertebrate host includes rodents, dogs, cats, and humans. It is endemic to the tropical and warm temperature zones of Central and South America, Africa, the Middle East, the Indian subcontinent, and many countries in the Mediterranean basin.[1-3]

Leishmaniasis of the eyelid is uncommon. The highest incidence has been reported in Algeria, where it has been described in 2–5% of all cases of facial leishmaniasis.[4] As there have been only three previous reports of eyelid leishmaniasis in visitors to endemic areas in the English literature,[5-7] it has been suggested that the rarity of eyelid infestation is due to eyelid movements preventing the fly vector from biting the skin in this area.[5]

We report a case of eyelid leishmaniasis occurring in a patient with reduce lid movements due to a chronic progressive external ophthalmoplegia.

## Case report

A 46-year-old Caucasian female developed a papule on her left upper eyelid in December 1988 while visiting rural Yemen. She stayed in a mountainous district near Ta'izz (syn. Taiz). The patient had a documented past history of chronic progressive external ophthalmoplegia and had presented as a teenager with bilateral ptosis. Her unaided visual acuity was recorded as 6/24 right and 6/18 left prior to her trip to the Yemen. Her corrected acuity was only one Snellen line better in each eye. Levator palpebrae superioris function measured less than 2 mm in each eye. There was bilateral inferior corneal exposure and lower facial weakness. She had bilateral total external ophthalmoplegia and pigmentary retinopathy. Electroretinographic responses to blue and white scotopic, photopic, and flicker stimuli were all within normal limits. Goldmann fields were full. An edrophonium (Tensilon) test gave a normal result. Her electrocardiogram did not show any conduction defect.

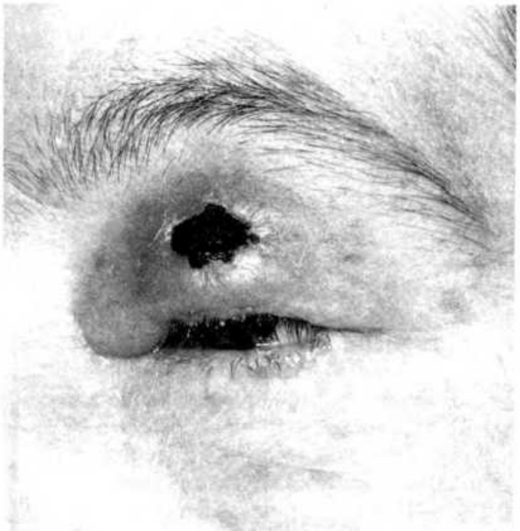

*Figure 1 Appearance of the left upper eyelid eight weeks after the onset of symptoms.*

The eyelid lesion enlarged slowly over the next four weeks and the entire lid became oedematous, with a small ulcer developing in the centre. Her vision was unchanged, and systemically she was in good health. On returning to the United Kingdom she was treated with 2 g of flucloxacillin daily in divided doses for four weeks. The lesion persisted despite antibiotics, and she was referred to our eye casualty for further treatment. Oriental sore was suspected and she was therefore referred to a dermatologist.

Eight weeks after the onset of symptoms the area of left upper lid induration was recorded as 25 mm in diameter while a central area of ulceration measured 5 mm (Fig 1). There was no mucosal involvement. Systemic examination did not reveal any lymphadenopathy, hepatomegaly, or splenomegaly. Her haemoglobin, white cell count, differential count, and blood film were all normal. A biopsy was taken from the non-ulcerated edge of the lesion, and cutaneous leishmaniasis was diagnosed histologically on haematoxylin and eosin staining of a formalin fixed specimen. This showed an infiltrate of plasma cells and pale histicocytic cells containing multiple Leishman-Donovan bodies in the dermis. No further identification of the species was made.

She was treated with sodium stibogluconate (Pentostam) 10 mg/kg body weight daily for 21 days, with regular monitoring of her hepatic transaminases and ECG. She had no adverse reactions to treatment. The ulcer healed two months after treatment, and the residual oedema settled two months later (Fig 2).

## Discussion

Old World leishmania causes four distinct forms of cutaneous disease depending on the degree of the host's cellular immune response. Oriental

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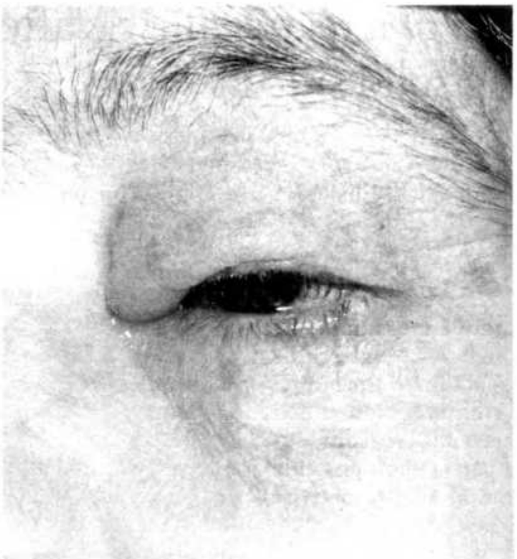

*Figure 2 Appearance of the left upper eyelid four months after the onset of symptoms. The residual lid oedema did not resolve for a further two months.*

sore is the commonest form. It causes an ulcer which usually heals within six months. Leishmaniasis recidiva and diffuse cutaneous leishmaniasis are chronic recalcitrant forms of cutaneous leishmaniasis seen in subjects with hyperergic and anergic responses respectively. The development of immunity following infections with visceral leishmaniasis may be accompanied by the occurrence of post-kala-azar dermal leishmaniasis.[1]

Old world cutaneous leishmaniasis (without visceral involvement) is caused by *Leishmania tropica*, *L major*, *L infantum*, and *L aethiopica*.[1-3] It is possible that any of these strains caused this infection, as the *Leishmania* strain was not identified and there is limited knowledge about the strains of leishmaniasis present in Yemen.[2] Epidemiological studies have demonstrated the presence of *Leishmania tropica*, *L donovani*, and *L infantum* in rural, coastal, and mountainous Yemen.[8] Enzyme linked assays used in this recent study showed that *L tropica* (strain LON 71) caused all cases (24/24) of cutaneous leishmaniasis tested in the study area.

Cutaneous leishmaniasis should be considered in the differential diagnosis of eyelid ulcers, abscesses, or nodules in patients who have been to areas endemic for leishmaniasis. It may mimic chalazion, skin tumours, or epidermoid cyst.[4 6 9 10] It is important for medical staff to be aware of the prevalence of leishmaniasis with increasing international travel and also to know that the incubation period may extend to several months.

Treatment includes control of secondary infection, the intralesional or systemic administration of antimony, and cryotherapy.

Morgan suggested that the rarity of eyelid infestations was due to movement of the upper eyelid preventing the sandfly vector from inoculating this otherwise exposed site.[5] As this patient had virtually absent levator function, her case gives further support for this hypothesis.

We thank Mr G Sutton for his permission to report this patient.

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# Preserved action of a rectus muscle after transection by an encircling solid silicone band

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**Abstract**

**We present a case of anterior migration of a solid silicone band through a lateral rectus muscle. In this patient the action of the lateral rectus was preserved, and this is demonstrated photographically. The possible reasons for this rare complication and the possible mechanism by which lateral rectus activity remained intact are explained.**

Exposure of implanted material after retinal detachment surgery is a known and rather common complication. It happens usually with radial buckles, but also with encircling elements. Anterior migration of an exposed solid silicone band eroding through a rectus muscle without causing disturbances in ocular motility is rare, and we believe this is the first photographic report of this rare complication of retinal detachment surgery.

## Case report

A 57-year-old man was referred to our department with aphakic retinal detachment in the right eye. In the year prior to his admission he underwent extracapsular cataract extraction, with vitreous loss in both eyes. This was followed by aphakic retinal detachment in both eyes, which was successfully repaired in the left eye. In the right eye he had three unsuccessful retinal detachment operations, after which he was referred to us. We performed vitrectomy and silicone oil injection combined with placement of a new radial sponge in the right eye, and the retina reattached.

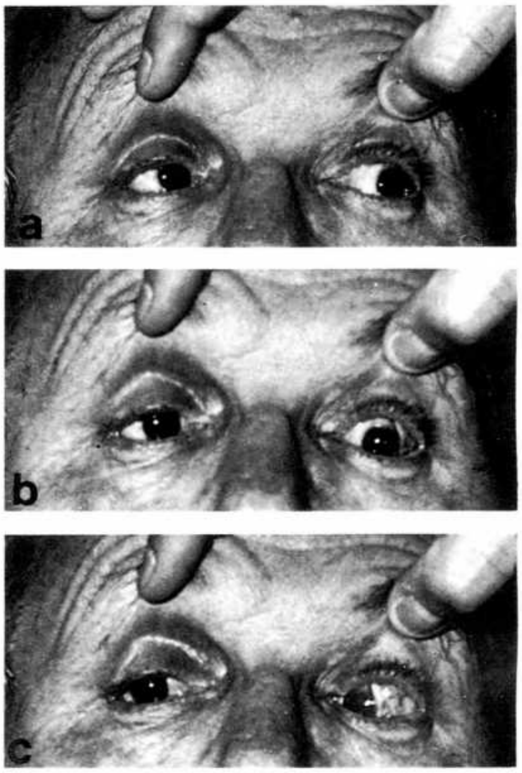

*Figure 2 The eyes are shown in gaze to the left (a), primary position (b), and gaze to the right (c). Full range of the left lateral rectus and lack of restriction on gaze to the right are demonstrated.*

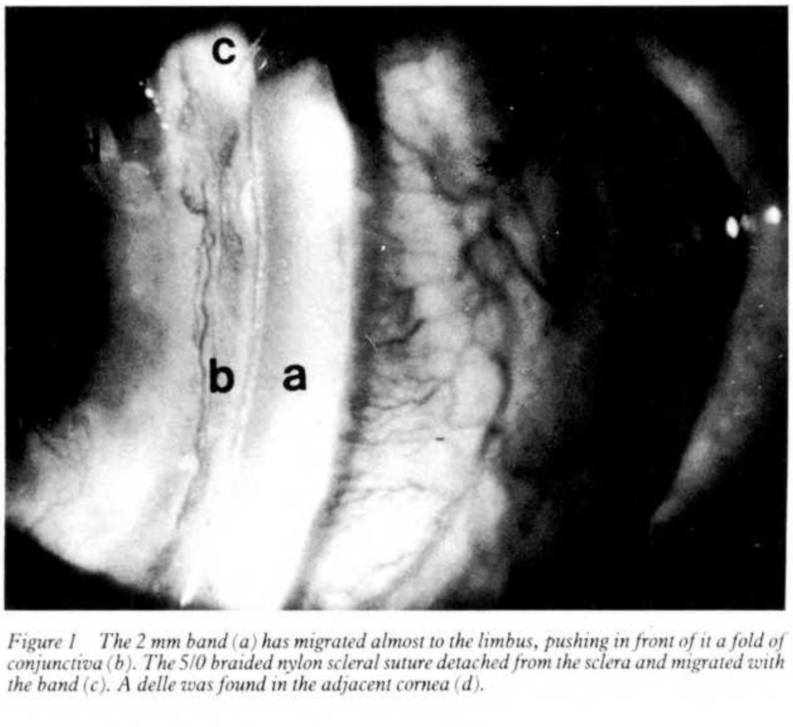

*Figure 1 The 2 mm band (a) has migrated almost to the limbus, pushing in front of it a fold of conjunctiva (b). The 5/0 braided nylon scleral suture detached from the sclera and migrated with the band (c). A delle was found in the adjacent cornea (d).*

Two months later an asymptomatic inferior retinal detachment was observed in his left eye. Vitrectomy, air exchange, removal of the previous encircling 5 mm silicone sponge, and placement of an encircling 2 mm solid silicone band and a radial silicone sponge were performed, and the retina reattached. A few weeks later the new radial sponge became exposed and was removed.

Two years after his last operation the patient returned complaining of mild discomfort in his left eye. On examination the 2 mm band was seen exposed on the temporal side of the limbus, pushing forward a fold of conjunctiva and causing a large delle on the corneal side of the band. Part of a torn scleral suture was seen tied to the band (Fig 1). Remarkably, lateral rectus movements were completely preserved (Fig 2). Under topical anaesthesia the exposed part of the band was resected. After a few days on topical dexamethason phosphate 0·1% four times a day and chloramphenicol 5% ointment three times a day the delle healed, and the eye became asymptomatic. At his most recent follow-up, in December 1988, the retina remained attached, and he was asymptomatic.

## Discussion

Anterior migration of a solid silicone band may occur if it is tight, placed anteriorly to the equator, and insufficiently anchored to the sclera. As an anterior sliding band slowly erodes through the tendon of one or more recti muscles, there is sufficient time for the muscles to reattach spontaneously with scar tissue behind the migrating element.[1] We believe that such was the case with our patient. An alternative explanation might be that the band may have been placed external to the muscle. We do not believe this is possible because of the expertise of the surgeon (GT), and because the band was sutured to the sclera, as evidenced by the displaced suture attached to the band. It is inconceivable that the surgeon would not have noticed external placement of the band while he was suturing the band to the sclera close to the muscle.

It is remarkable that there was no limitation of the horizonatal eye movements, and that the lateral rectus retained its full range of movement. This indicates that the tendon was not recessed from its insertion and that the scar tissue which kept it in place did not limit its action.

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# LETTERS TO THE EDITOR

## Bilateral simultaenous spontaneous acute angle closure glaucoma in a herpes zoster patient

SIR,—Acute angle closure glaucoma is very common and may occur in predisposed eyes, frequently following precipitating conditions. However, the vast majority of patients present with unilateral acute angle closure, and the occurrence of simultaneous spontaneous attack is extremely rare. We have managed a case of simultaneous spontaneous bilateral acute angle closure in a patient with T-2 dermatome herpes zoster.

A 61-year-old woman was referred to our clinic because of severe headache, vomiting, and decreased visual acuity for two days prior to admission. Five days earlier a T-2 dermatome herpes zoster (Figs 1 and 2) was diagnosed and a course of oral acyclovir (Zovirax), 200 mg five times a day, was begun. On examination her visual acuity was counting finger OD and hand motion OS. The intraocular pressure on applanation tonometry was 48 mmHg OD and 58 mmHg OS. Both eyes had ciliary congestion, oedematous cornea, shallow anterior chamber, and mid dilated pupils. The lens showed a +2 nuclear sclerosis cataract. The retina was attached and the optic nerve heads showed some hyperaemia.

The patient was treated with mannitol, acetazolamide 500 mg intravenously, pilocarpine 2%, and dexamethasone, and within 90 minutes the intraocular pressure was 10 mmHg OU. During the following two days laser iridotomies were performed in both eyes, and today in both eyes the best corrected vision is 20/30. Intraocular pressure is 14 mmHg OD and 13 mmHg OS, the fields of vision are normal, and laser iridotomies are patent.

Acute angle closure glaucoma is frequently precipitated by mydriasis caused by parasympathomimetic and sympatholytic agents, dim illumination, and prone position. Emotional stress may also precipitate it.[1] Even though in most individuals presenting with acute angle closure both eyes share the predisposing characteristics, only one eye is involved. Simultaneous presentation is rare but has been described.[2]

This unusual presentation of simultaneous bilateral involvement in a patient with herpes zoster suffering agonising pain focuses our attention on another possible precipitating factor. Pain, possibly through increased sympathetic tone, and subsequent mydriasis might initiate a resonse resulting in angle closure in predisposed individuals.

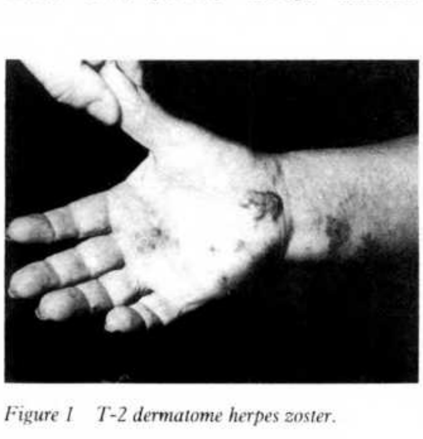

*Figure 1* *T-2 dermatome herpes zoster.*

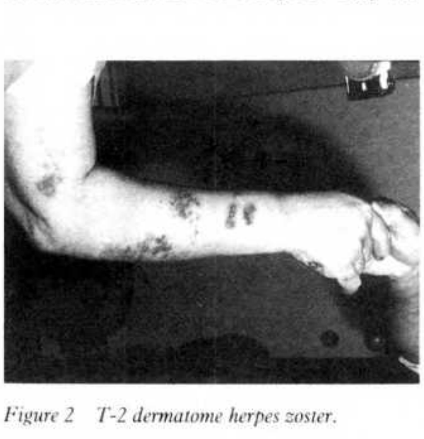

*Figure 2* *T-2 dermatome herpes zoster.*

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## The association of Fuchs's corneal endothelial dystrophy with angle closure glaucoma

SIR,—We read with great interest the article by Pitts and Jay.[1] We report the results of our study on this subject, which support their observation.

The association of Fuchs's corneal dystrophy with angle closure glaucoma is usually attributed to the oedematous thick cornea crowding the anterior chamber angle.[2-4] We have the impression that the acute angle closure glaucoma in patients with Fuchs's dystrophy is unrelated to the corneal oedema, since it often occurs long before the process of corneal decompensation. In order to verify this observation we performed a retrospective analysis on our patients who underwent perforating keratoplasty because of Fuchs's corneal dystrophy during the last 10 years. All the patients were re-examined and the following details recorded: age, sex, refraction before surgery (from patients' records or lensometer readings of the patients' oldest distance spectacles), history of angle closure glaucoma and peripheral iridectomy, axial length, and anterior chamber depth before surgery.

Twenty-three patients (15 females and 8 males, 53 to 95 years old) were operated on. Eight of them had undergone an iridectomy because of an acute attack of angle closure glaucoma one to 30 years before the development of corneal oedema. An additional three patients had a very narrow angle when first examined by us, and therefore prophylactic iridectomy was performed during the keratoplasty. Thirteen eyes had axial length shorter than 24·2 mm (mean 21·59, SD 0·80 mm) and anterior chamber depth less than 3·4 mm (mean 2·4, SD 0·24 mm). The means in the general population for axial length and anterior chamber depth are considered 24·2 mm and 3·4 mm respectively.[5] Seven had hyperopic refraction (mean 2·25, SD 1·34 dioptre). Only one eye of each patient was considered in the calculations.

In summary, of the 23 patients 11 had problems related to angle closure glaucoma. The acute attack occurred in eight of them long before the clinical symptoms of Fuchs's dystrophy. This rules out the possibility that the attack was caused by the oedematous cornea crowding the angle. The probability that the corneal damage was caused by the acute rise of pressure and/or the iridectomy seems unlikely. In six of the eight patients corneal endothelial damage characteristic of Fuchs's endothelial dystrophy was present in the fellow eye which had not sustained an acute attack of angle closure glaucoma.

It is obvious from Pitts and Jay's series, and from the additional information presented in this report, that there is a high incidence of axial hypermetropia, shallow anterior chamber, and angle closure glaucoma in patients with Fuchs's corneal dystrophy. The clinical evidence suggests that there is no causal relationship in either direction, and it is likely that the association arises from a common factor leading to both conditions by genetic linkage.

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## Topical beta blockers and serum lipoproteins

SIR,—With reference to the paper by West and Longstaff,[1] it was reassuring to read that topical timolol was found 'to have no significant adverse effect on serum lipoprotein levels.', However, another recent paper came to a different conclusion that topical timolol significantly reduced plasma high-density lipoprotein (HDL) levels.[2] The difference in the results of these two studies may be due to the following reasons.

(1) Coleman *et al*[2] studied normal, healthy volunteers while West and Longstaff[1] examined glaucoma patients. The effect of topical timolol on serum lipoproteins in elderly glaucoma patients (mean age 67·5 years) may be different from that in young, healthy subjects (mean age 35·2 years).

(2) It is well known that the compliance of patients with glaucoma drug therapy is often less than ideal.[3] Since patient compliance with topical timolol appears not to have been objectively assessed in the study by West and Longstaff,[1] this may have affected the overall results.

(3) When testing for serum lipoproteins, two separate fasting blood samples, taken on different days, have been recommended to take account of the large intraindividual variations

in lipid values.[4] The reliance on a single test value[1] may have affected the results.

The authors[1] use the serum triglycerides concentration to establish adequate study power to detect a clinically significant change in serum lipoproteins due to topical timolol. It would be more helpful if they were to mention if their study had an adequate power to detect a clinically significant change in the HDL concentration, since it bears a well established inverse relation to coronary heart disease, unlike serum triglycerides, the role of which is unclear.

We suggest that it is premature to rule out clinically important adverse effects on serum lipoprotein levels by topical beta blockers on the basis of the study by West and Longstaff.[1] This is particularly so because the majority of patients with open angle glaucoma throughout the world are commenced on topical β-adrenergic antagonists. A significant number of them will have coexistent risk factors for coronary heart disease. In these patients even a small reduction in serum HDL concentration and/or increase in serum cholesterol may have a significant effect on the incidence of coronary heart disease. Hence a more comprehensive study of a larger number of glaucoma patients involving different ophthalmic centres, if necessary, would be useful to establish the effects of various topical beta blockers on serum lipoprotein levels.

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1 West J, Longstaff S. Topical timolol and serum lipoproteins. *Br J Ophthalmol* 1990; 74: 663–4.
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## Reply

SIR,—We appreciate the interest shown by Raj and Joyce in our paper.[1] We agree that the effects of topical timolol on serum lipoproteins in elderly patients may differ from that in young healthy subjects. However, as those people in the general population taking timolol therapy are glaucoma patients and not young healthy subjects, we felt it more relevant to study the effect in the former group.

Assessment of compliance with eyedrop therapy is always difficult. The method used by Coleman *et al*[2] does provide a means of quantitating the number of drops expressed from each bottle, but does not take account of such factors as drops missing the eye and inadvertent or deliberate expression of drops from the bottle. Because our study was carried out over a short time period of 15 weeks on patients newly started on timolol, who had the importance of their therapy carefully explained, we would hope to have had good compliance.

Intraindividual serum lipoprotein levels are known to suffer from a large coefficient of variation which can be reduced by increasing the number of samples from an individual. However, when comparing the mean of a group of individuals at one time with that at a later time intraindividual variation is accounted for in the statistical analysis. Our 95% confidence intervals for triglyceride levels at five weeks of −0·22 to +0·14 mmol/l allows us to say with 95% confidence that triglyceride levels do not rise by more than 9% at five weeks. From systemic studies one would expect the reduction in HDL levels to be half this (ie, 4·5%), a relatively small reduction. However, as Raj and Joyce point out, even a small reduction in serum HDL levels may have a significant effect on the incidence of coronary heart disease.

A larger study demonstrating narrower confidence intervals would, we agree, be useful.

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1 West J, Longstaff S. Topical timolol and serum lipoproteins. *Br J Ophthalmol* 1990; 74: 663–4
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## Seeing stars

SIR,—My first few months as a first-year ophthalmology resident literally had me seeing stars. While attempting slit-lamp transillumination on a patient with pseudoexfoliative glaucoma I suddenly focused in on a perfectly symmetrical six-pointed star with a circular centre. Its location seemed to be somewhere between the corneal endothelium and the lens but was difficult to localise precisely. After showing my finding to all the other residents in the clinic (who had never seen or heard of this star before) and extremely excited about the possibility of having this ophthalmological phenomenon named after myself, I spent the next two evenings searching through my newly purchased Duane's textbook to make sure this star had not previously been described.

Finally, a not-so-convinced attending sat down at the slit-lamp and manipulated the settings until he was able to project the tiny image of the above described six-pointed star on to a piece of paper placed in front of the slit-lamp. Since then I have called the Haag-Streit Bern slit-lamp service centre in New Jersey which solved the mystery. Indeed, all of the newer models of Haag-Streit Bern slit-lamps incorporate a filter in the 's' or small aperture setting which is described as a 'target' with fixation star particularly suitable for examining fixation in amblyopia.' I suppose I will have to keep searching for an ophthalmological phenomenon to name after myself.

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## Paget's disease and angioid streaks: one complication less?

SIR,—I read with interest your editorial[1] on the association of Paget's disease in angioid streaks, and most particularly your comments regarding the article which appeared in the *American Journal of Ophthalmology*.[2] Not only were the angioid streaks confirmed by colour fundus photographs, but by fluorescein angiography, and then by careful histological serial sections which correlated the clinical appearance of the angioid streaks with linear breaks in Bruch's membrane.

With regard to the association of angioid streaks with Paget's disease, we performed a complete ophthalmological evaluation on 50 patients with clinically active Paget's disease of the bone, and found angioid streaks in five of these patients. Interestingly, there was a higher incidence of angioid streaks in those patients with clinically active skull involvement.

The patients in our survey all had increased 24-hour production of urinary hydroxyproline and an alkaline phosphatase of at least twice normal. Therefore it is not surprising that a group of unselected and probably asymptomatic patients with Paget's disease should demonstrate a lower incidence of angioid streaks. In addition, Dabbs and Skjodt only performed fluorescein angiography on selected patients. Angioid streaks may be difficult to detect on routine ophthalmoscopic examination.

We agree that the coexistence of pseudoxanthoma elasticum may be difficult to rule out. However, the presence of even one patient in this unselected group of 70 patients chosen only because of their past exposure to canine distemper could be significant, particularly in the light of our findings that the patients with active Paget's disease of the bone were more likely to show evidence of angioid streaks. It seems Terry's original observation probably is correct.[3] Our findings support Terry's original observation. We assume that in 1934 those patients known to have Paget's disease had obvious clinical manifestations of the disease, as opposed to the patients reviewed by Dabbs and Skjodt, in whom the diagnosis of Paget's disease may have been less obvious.

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# BOOK REVIEWS

**Year Book of Ophthalmology 1988.** Eds J Terry Ernest, Thomas A Deutsch. Pp 268. £43.50. Wolfe Medical: London, 1988.

The 1988 *Year Book* follows the traditional format of this popular series. Fifty three ophthalmic and specialty-related journals were reviewed, and the editors selected articles which reported the most interesting and innovative material published in 1988. The book is divided into 11 chapters dealing with all the ophthalmic clinical subspecialties as well as basic sciences. The chapters are introduced by short review articles by well known authorities in their fields. The reviews are followed by abstracts of 20 to 30 original papers. After each abstract there is a short (and often amusing) comment by Dr Deutsch.

As all *Year Books*, the 1988 edition makes very interesting reading. It is the last in the series under the present editors, and hopefully their successors will continue to distil the ever increasing volume of ophthalmic literature in this efficient yet enjoyable format.

Z GREGOR

**Surgery of the Eyelids and Orbit: An Anatomical Approach.** By Bradley N Lemke, Robert C Della Rocca. (Pp 322; £92.) Prentice-Hall: Hemel Hempstead, Herts. 1990.

This new book is a textbook of surgical anatomy rather than a comprehensive textbook of surgery, and in this respect the title is misleading. The anatomy of the midfacial tissues is described in detail and clinical surgery is discussed within this framework. The authors are well known for their publications in ophthalmic plastic surgery and anatomy in particular.

The book is divided into five sections: osteology, nose and paranasal sinuses, lacrimal excretory system, the eyelids, orbital anatomy, and surgery. Each section begins with a general subsection on clinical considerations. Specific clinical points are made in the anatomy subsections and selected operations are described. Each section has an extensive bibliography.

It is the anatomy which is of greatest value in this book. The text is readable and well researched. The illustrations are good black-and-white photographs of osteology and cadaver dissections backed by clear line drawings. The clinical and surgical parts of each section are less consistent and do not always fit comfortably within the anatomical framework of the book. This leads to a discursive style which lacks a systematic arrangement of clinical information Acute dacryocystitis and lacrimal system tumours, for example, appear in the subsection on the lacrimal pump; the assessment of ectropion is found with lateral canthal repair. This scattering of clinical information means frequent reference to the index to gather a topic together.

The authors have been very selective in their choice of recommended operations, especially in the section on the eyelids. Only transposition of orbicularis and (in a different subsection) repair of the lower eyelid retractors by a skin approach are offered for the correction of entropion. The whole of ptosis surgery is covered by anterior approach levator repair or resection. Muller's muscle surgery is limited to its excision in thyroid ophthalmopathy. Eyelid reconstruction is hardly mentioned. Operations which are included are, however, well described and illustrated.

This is an attractively produced book in hardback which will appeal mainly as a text on surgical anatomy. Those looking for a systematic, comprehensive coverage of practical ophthalmic plastic surgery will be disappointed.

A G TYERS

**The Eye in Infancy.** By Sherwin J Isenberg Pp 522. £45.00. Year Book Medical: London, 1989.

This is a multiauthor textbook dealing entirely with the eye in the first year of life. It succeeds well in its aim to concentrate on the eye in infancy. The first section, on general considerations in the newborn eye, considers anatomy and physiology of the eye at birth and problems of assessing visual acuity. There is an excellent second section on congenital malformations which are evident at birth or soon after and a third section on acquired ocular disorders of the newborn. The book concludes with a discussion of the newborn eye in systemic disease.

I would pick out the sections on retinopathy of prematurity as being exceptionally helpful and easy to read, giving an excellent up-to-date review of this subject. The chapters on chromosomal abnormalities and anomalies of the eyelid are also outstanding. This book is well illustrated and practical. There are excellent bibliographies at the end of each chapter.

This is one of the best multiauthor American textbooks that has come my way for some years, and I can fully recommend it to every ophthalmologist in training. I think it will become a standard reference work on the eye in the first year of life.

ALAN MUSHIN

**Current Ocular Therapy.** Vol 3. Eds Frederick T Fraunfelder, F Hampton Roy. Pp 792. £55.00. Saunders: London, 1990.

This is an unusual book. Since it is the third edition, I should know it already, but hitherto have been unaware of it. At a first glance it would appear to be potentially an extraordinarily useful volume to have available for reference, preferably in the consulting room or not far away, and especially if one were to encounter a condition one did not meet often and for which therefore were uncertain of the best treatment. As a practical test I looked up five conditions at random in the index of the *System of Ophthalmology* (which although unsurpassed for comprehensiveness is not strong on treatment) and then attempted to find them in this book. Hypersensitivity of the conjunctiva, osteitis fibrosa, heterochromic cyclitis, diabetic retinopathy, and craniopharyngioma were the conditions randomly picked out. The book contained informative articles on all five of the sample subjects, though the somewhat obscure 'osteitis fibrosa' of the *System* seemed to have changed its name to Engleman's disease and several closely related syndromes. Extending the scope of the test by referring to the advice given in the conditions chosen, one is not disappointed. In my opinion this is an extremely useful reference book and will prove of value especially in busy ophthalmological hospital departments

R SMITH

**Progress in Sensory Physiology 10.** Eds H Autrum, D Ottoson, E R Perl, R F Schmidt, H Shimazu, W D Willis. Pp 124. DM 124.00. Springer-Verlag: Heidelberg, 1990.

This informative book attempts a highly ambitious task. In essence it surveys the morphological, physiological, and pharmacological background to the synaptic circuits in the central visual system and discusses the ways in which the neurones in these circuits are influenced by the neuromodulatory systems arising in the brain stem and basal forebrain. The material is subdivided into four main sections. These cover the basic anatomy and physiology of the visual pathway and neuromodulatory systems of the brain stem and basal forebrain, the neurotransmitters involved, and the way the core systems generate state-dependent changes in the visual cortical and thalamic circuits. This work cannot be regarded as an introduction for workers outside the field: a good background knowledge in all the main areas is essential for anyone attempting to follow the main arguments. Its particular strengths are that it reviews the background literature in each of the main areas and attempts a synthesis phrasing the action of the brain stem and basal forebrain modulatory systems in the context of neuronal function in the visual system

One has to say that it is not an easy work to read. Much of the information is presented in a very brief and notelike fashion, and one needs to be very interested in the material to follow through each section with patience. A level of caution is required, because some statements are clearly incorrect and misleading. For example, one learns on p 22 that in the visual cortex: 'At variance with the projections of spiny stellate cells, the axons of pyramidal neurones synapse mainly with aspiny or partially spined neurones.' This is quite incorrect. The reference cited deals with a very specific connection made by layer VI cells in layer IV of the visual cortex, and even here the conclusion is open to some debate. The majority of pyramidal cell connections are with other spiny cells.

The account of the circuitry and function in the lateral geniculate nucleus was, I felt, more balanced than the treatment of the cortex, and the main issues were nicely summarised The discussion of the intracellular data regarding GABAergic mechanisms is both clear and thoughtful. The main focus of the book, however, is one that leads the reader to consider the state-dependent changes in these processes. The effects mediated by the cholinergic input to the lateral geniculate nucleus from the peribrachial region of the pedunuclo-pontine nucleus are particularly intriguing because there are some interesting conflicts in the available data. The main interest for ophthalmologists may well be in this section of the book covering the mechanisms controlling and modifying the retina's access to the brain. Overall I would recommend this short book only to those with a particular interest in the field. It is far too detailed and specialised to help those meeting the topics covered for the first time.

A M SILLITO

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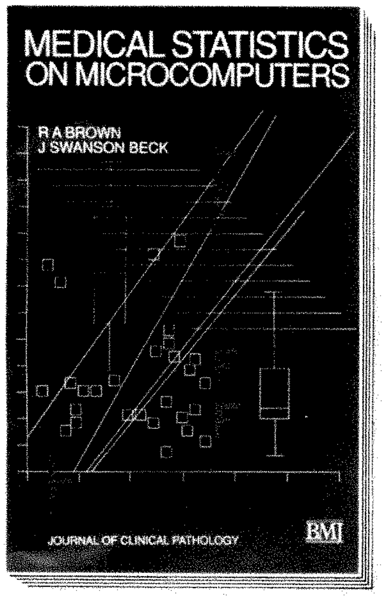
⁂ All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MASTERCARD, VISA or AMERICAN EXPRESS), stating card number, expiry date and your full name.

# NOTE

## Glaucoma meeting

A glaucoma meeting in honour of Mr Redmond Smith, editor of the *BJO*, will be held on 4 October 1991 at the Institute of Ophthalmology, 17–25 Cayton Street, London EC1V 9AT. The organiser is Mr Roger Hitchings. Registration fee: £95 (to include buffet lunch, refreshments, and evening reception). Details from Mrs Sharon Robinson at the Institute (tel: 071 387 9621 ext 269, fax 071 490 8971).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# How is no longer a problem – but there's still which and why

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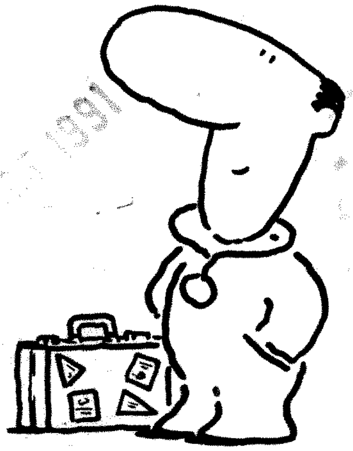

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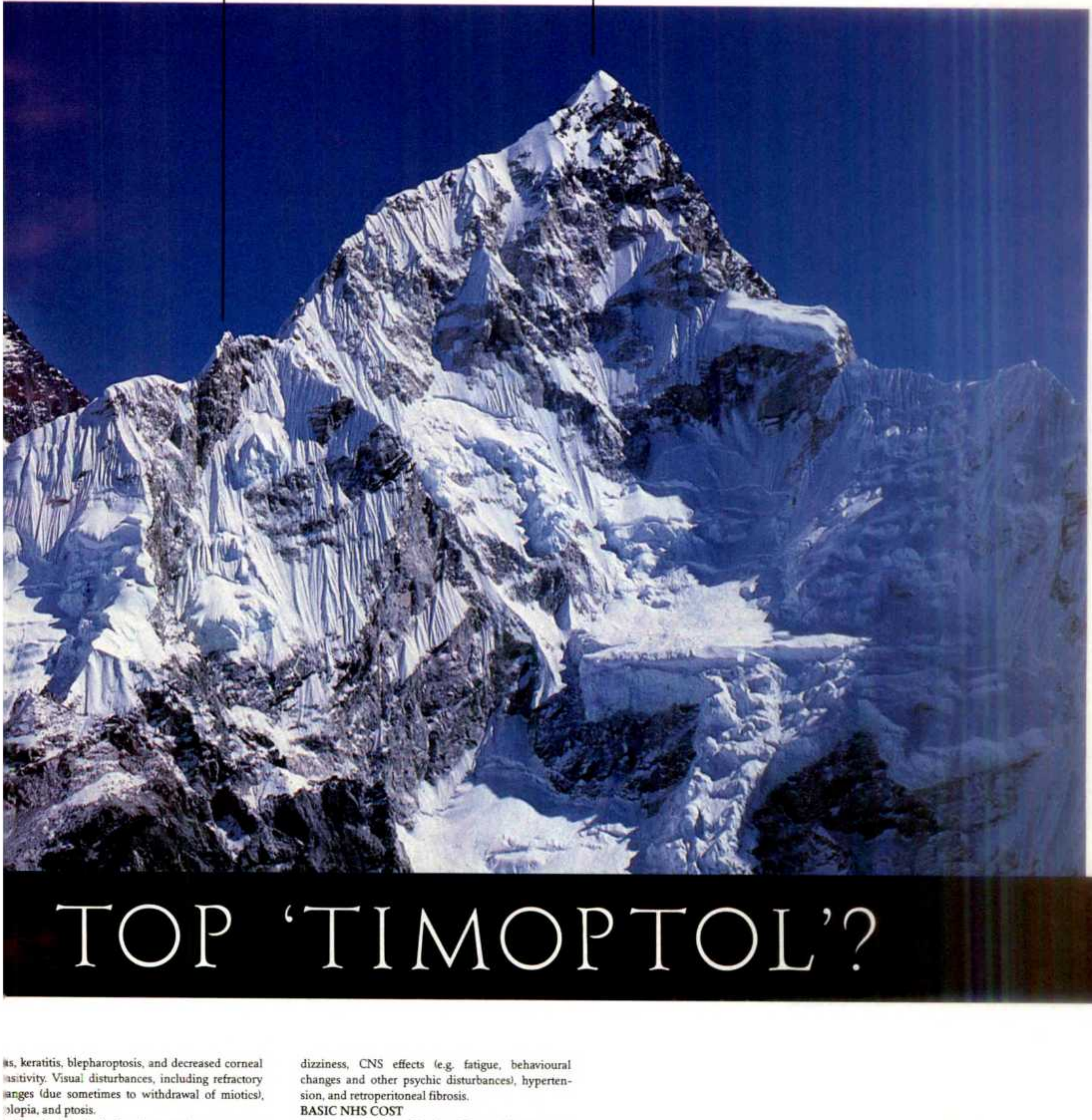

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## *Editorial*

# Video laser ophthalmoscopy in diabetes

If the histopathological study of diabetic retinopathy is a relatively new activity following on the improved life expectancy of diabetics after the discovery of insulin, then the study of the vascular dynamics of the retina is even newer.

It has been known for many years that the capillary-free zone round retinal arterioles in diabetics tends to be enlarged, but the early knowledge was based on static post-mortem histological material where the retina was injected with Indian ink and mounted flat on glass.[1] Several ingenious attempts to demonstrate the dynamics of flow in the small vessels of the retina have been described, including a study of the entoptic impression of the paramacular circulation[2] and laser Doppler velocimetry,[3] but neither of these methods gave anything approaching the graphic demonstration of the retinal capillary flow afforded by the combination of fluorescence angiography and the scanning laser ophthalmoscope as described by Arend and colleagues in the present issue. It appears that the resolution of the system is so good that two different densities of fluorescence are detectable within the blood column, the less fluorescent probably corresponding to rouleaux of red blood cells and the more fluorescent to plasma. Assuming that this is right, and there seems little reason to doubt it, one is then in a position to make direct measurements of the velocity of the rouleaux. It is also possible for measurements of the foveal avascular zone (FAZ) and the perifoveal intercapillary areas (PIA) (in effect the density of the capillary bed) to be estimated by this technique.

Over the years the ordinary ophthalmologist has been somewhat baffled by the complexity of some of the attempts to explain what is going on in diabetic retinopathy – the role of pericytes, the reason for thickening of the basement membrane, the origin of microaneurysms, the part played by variations in viscosity, irregularities in vascular calibre, arterial blood pressure, and so on. The impression gained by reading the early histopathological work was of a gradual accumulation of foci of occlusion of prevenous capillaries with consequent backing up of the flow in the 'upstream' areas of the bed leading to slow flow, leakage of lipids through the capillary walls, and microaneurysm formation, the ischaemia associated with this gradual process of vascular disorganisation leading ultimately to neovascularisation.

Apart from the fact that the reason for the capillary occlusions was not obvious the rest of the scenario was reasonably convincing, so it was a great delight to read in the current paper that the authors agree that the 'development of diabetic retinopathy is, at least in part, due to progressive capillary occlusion and decreasing capillary perfusion.'

In the blue light entoptic study of Rimmer *et al*[2] the principal finding was a tendency to slowing of velocity of the blood in the perifoveal capillaries both in comparison with controls and over a time interval of several years; in other words the slowing appeared to be progressive. Several possible reasons for the phenomenon were discussed in that paper, including alterations in retinal metabolic rate, a decrease in red cell deformability, and an increase in red cell aggregation, but none of those factors were measured at that time.

The current study confirms the reduction of the blood flow velocity but offers a further interesting piece of information. If the mean capillary velocity were to be reduced in comparison with normal velocity because of abnormalities in the vessels themselves, owing to variations in calibre in particular, one would have thought that the diabetics would be likely to show wider variations in velocity from site to site in the retina as compared with normal persons. However, this was not the case; the coefficient of variation of the velocity showed no significant differences between diabetic and normal subjects.

This would suggest that, whatever the cause of the slowing, it ought to be detectable in the blood itself rather than the capillary bed. Whether the sensitivity of this 'smart' system of looking at the circulating blood can be increased sufficiently to determine differences in the characteristics of the flowing blood itself, such as the size and shape of the rouleaux, the way they roll and tumble, and so on, will be a fascinating future prospect.

It is of interest that the present authors found reduction of velocity even in diabetics with little or no retinopathy, and there did not seem a strong correlation between greater slowing and greater retinopathy. This was in contrast to the rather dramatic increase of the PIA and FAZ with severer grades of retinopathy.

REDMOND SMITH

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ORIGINAL ARTICLES

# Retinal microcirculation in patients with diabetes mellitus: dynamic and morphological analysis of perifoveal capillary network

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## Abstract

**The new scanning laser technique allows one to quantify the retinal microcirculation. A digital image analysing system was used to study capillary blood flow velocities and morphological parameters of perifoveal intercapillary areas and foveal avascular zones in normal and diabetic subjects. Diabetic patients showed a significant reduction in capillary blood cell velocities in comparison with normal subjects. Perifoveal intercapillary areas and foveal avascular zones were significantly increased in all stages of diabetic retinopathy, and both parameters increased with progressing diabetic retinopathy. Significant changes in the perifoveal intercapillary areas were observed between normal subjects and patients with no retinopathy.**

The combined vascular and haemodynamic pattern in diabetic patients is characteristic, though no single feature in the vascular bed has any absolute relation to the diabetic condition. The earliest detectable morphological changes in diabetic retinopathy are microaneurysm and capillary closure.[1] Development of diabetic retinopathy is, at least in part, due to progressive capillary occlusion and decreasing capillary perfusion.

The scanning laser technique[2,3] in combination with an image analysing system was used to assess the morphological and haemodynamic changes in diabetic retinopathy. Quantitative measurements of flow velocities in perifoveal capillaries[4] and morphological data of the perifoveal capillary network were obtained by this technique. To investigate whether retinal blood flow velocities and morphological parameters change in more severe retinopathy we determined capillary blood flow velocities (v), foveal avascular zones (FAZ), and perifoveal intercapillary areas (PIA). Forty eight patients with diabetes mellitus were included in this study.

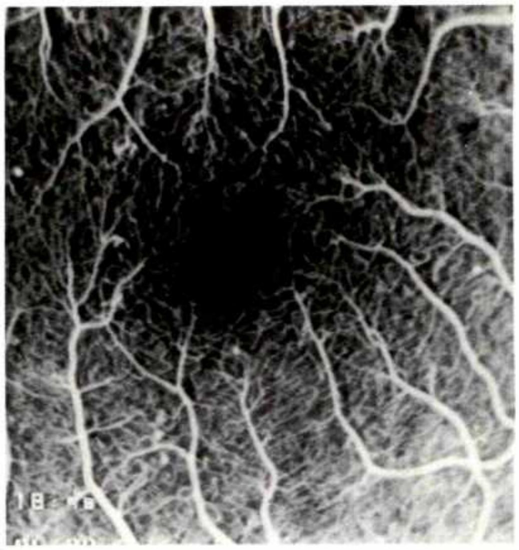

*Figure 1 Digital fluorescein angiogram of the perifoveal network of a 28-year-old diabetic man with mild background retinopathy. Duration of diabetes mellitus was 10 years.*

## Materials and methods

### SUBJECTS

In 48 diabetic patients (23 male and 25 female, age 19 to 67 years) 48 eyes were examined. There were 25 insulin dependent and 23 non-insulin dependent patients. Eighteen patients had a history of systemic hypertension. The duration of diabetes was from 1 to 34 years. The eyes studied had a visual acuity of 6/12 or better, minimal or no refractive error (between +1·0 and −1·0 D), and intraocular pressure of less than 20 mm Hg. Different stages of diabetic retinopathy were found and defined by means of ophthalmoscopy, fundus photography, and angiography. Four retinopathy levels were used: (1) no retinopathy (NDR); (2) mild to moderate non-proliferative retinopathy (microaneurysms and dot haemorrhages only) (BDR); (3) preproliferative retinopathy (multiple cotton-wool spots, intraretinal microvascular abnormalities, venous beading, or areas of non-perfusion) (PPDR; and (4) proliferative retinopathy (PDR). Patients with ischaemic diabetic maculopathy were excluded from this study. Glucose metabolism was assessed by the blood level of haemoglobin Alc (glycosylated haemoglobin) (normal range: 4·3 – 6·0%) in all subjects.[5]

The characteristics of apparently healthy subjects[6] and diabetic patients are summarised in Table 1. The controls had no history of serious ocular or systemic disease. No significant differences between apparently healthy and

*Table 1 Details of patients*

| | *No.* | *Sex M/F* | *Age (years)* | *BP syst. (mm Hg)* | *BP diast. (mm Hg)* | *Duration of diabetes (years)* | *HbA1c (%)* |
|---|---|---|---|---|---|---|---|
| Healthy volunteers | 21 | 10/11 | 26 (4) | 126 (12) | 79 (11) | – | – |
| Diabetic patients | 48 | 23/25 | 42 (14) | 143 (23) | 86 (14) | 14 (8) | 8·1 (1·3) |
| | | | NS | NS | NS | | |
| NDR | 7 | 2/5 | 39 (18) | 144 (26) | 98 (21) | 4 (3·2) | 6·9 (0·8) |
| BDR | 17 | 10/7 | 43 (13) | 136 (19) | 82 (13) | 13 (9) | 8·6 (0·9) |
| PPDR | 10 | 4/6 | 46 (15) | 145 (24) | 86 (14) | 15 (8) | 7·9 (1·9) |
| PDR | 14 | 7/7 | 40 (12) | 145 (25) | 83 (8) | 18 (6) | 8·2 (1·3) |
| Significance | | | NS | NS | NS | p<0·01 | NS |

NDR: no retinopathy. BDR: mild to moderate non-proliferative retinopathy. PPDR: preproliferative retinopathy. PDR: proliferative retinopathy.
Standard deviations in parentheses.

diabetic subjects for the demographic data were observed. Between the four diabetic retinopathy stages only the duration of diabetes showed significant differences.

Ophthalmological examination included best-corrected visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry, indirect and direct funduscopy, and colour fundus photography. In all subjects video fluorescein angiography was performed by means of the scanning laser ophthalmoscope.

## METHODS

The measuring technique used is presented in detail elsewhere.[4,6] In the digital video fluorescein angiograms segments of low and high fluorescence can be observed moving through the perifoveal network. The segments of low fluorescence may correspond to erythrocytes (rouleaux formations), the high fluorescence segments to cell-free plasma. The sequences were processed off-line to evaluate the following parameters[6]:

(1) (*a*) capillary blood flow velocity (v); (*b*) coefficient of variation of capillary blood flow velocity (homogeneity index): CV (v); (2) foveal avascular zone (FAZ); (3) perifoveal intercapillary area (PIA).

The measurement of the capillary blood flow velocity in the perifoveal network is calculated off-line by frame to frame analysis. The measurement of flow velocity is based on the determination of transit time $\Delta t$ between two measuring points, separated by a known distance $\Delta s$. The velocity of the moving hypofluorescent segments was calculated as $v=\Delta s/\Delta t$ by image analysis. At least 15 vessels of each patient were measured for evaluating v. The velocities of 10 segments of low fluorescence were calculated in each vessel in order to decrease the influence of vasomotion, even if the flow appeared to be not pulsatile. Therefore, every value of the mean blood flow velocity (v) was the result of 150 single measurements. These 150 measurements were performed within in a time period of about 5 seconds in the arterial phase of the angiograms. In addition, the coefficent of variation for the blood flow velocity, CV(v), was calculated from these measurements. This parameter characterised the homogeneity of the perifoveal capillary blood flow velocities of each patient.

The area of the foveal avascular zone and the perifoveal intercapillary area in the perimacular network were calculated by image analysis. For the quantification of these morphological parameters five consecutive images were superimposed by the image analysing system. No segments of low fluorescence were visible in these images. The foveal avascular zone was determined by drawing round the foveal arcade with the cursor in the digital image. The area described by the cursor was calculated with the picture analysing system. After the FAZ was quantified, the perifoveal intercapillary areas were marked interactively by the same method. Within a circle of 5° round the fovea the area of 60 different intercapillary areas were measured in each angiogram. For each patient the mean

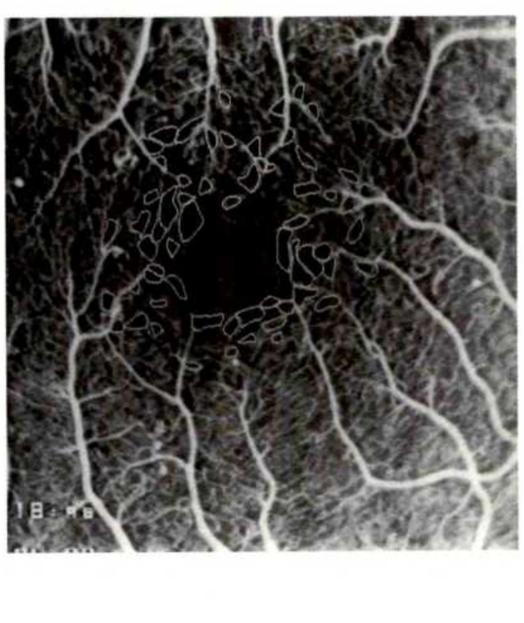

*Figure 2 Perifoveal network of a patient with mild background retinopathy and interactively marked perifoveal intercapillary areas.*

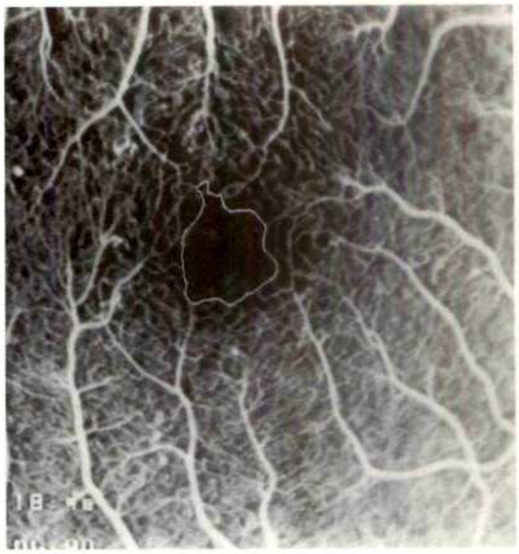

*Figure 3 Perifoveal network of a patient with mild background retinopathy and interactively marked foveal avascular zone.*

*Table 2 Retinal capillary blood flow velocities (v) and homogeneity index of apparently healthy subjects[6] and diabetic patients*

| | *No.* | *Blood flow velocity (mm/s)* | *Homogeneity index (%)* |
|---|---|---|---|
| Healthy volunteers | 21 | 3·28 (0·45) | 22 (5) |
| Diabetic patients | 48 | 2·43 (0·51) | 22 (10) |
| Significance | | p<0·01 | NS |

SD in parentheses.

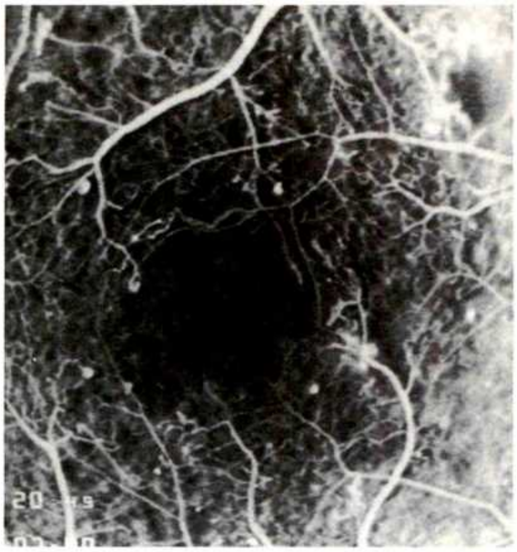

*Figure 4 Perifoveal network and foveal avascular zone of a 37-year-old diabetic man with preproliferative retinopathy. He had been suffering from diabetes mellitus for 22 years.*

area of perifoveal intercapillary areas was calculated from these 60 measurements.

In Figs 1-6 pictures of video fluorescein angiograms of two diabetic patients are shown. In these pictures the interactively marked parameters of perifoveal intercapillary areas (Figs 2, 5) and the foveal avascular zone (Figs 3, 6) are presented.

*Table 3 Perifoveal intercapillary areas (PIA) and foveal avascular zones (FAZ) of normal subjects and diabetic patients*

| | *No.* | *PIA* *($\mu m^2$)* | *FAZ* *($mm^2$)* |
|---|---|---|---|
| Healthy volunteers | 21 | 3900 (381) | 0·231 (0·06) |
| Diabetic patients | 48 | 8275 (2769) | 0·424 (0·24) |
| Significance | | p<0·01 | p<0·05 |

SD in parentheses.

*Table 4 Capillary blood flow velocity (v) and homogeneity index of diabetic patients divided in subgroups according to the retinopathy level*

| | *No.* | *Blood flow velocity (mm/s)* | *Homogeneity index (%)* |
|---|---|---|---|
| Healthy volunteers | 21 | 3·28 (0·45) | 22 (5) |
| NDR | 7 | 2·51 (0·88) | 25 (8) |
| BDR | 17 | 2·42 (0·40) | 24 (13) |
| PPDR | 10 | 2·28 (0·16) | 19 (7) |
| PDR | 14 | 2·27 (0·58) | 17 (5) |
| Significance | | NS | NS |

NDR: no retinopathy. BDR: mild to moderate non-proliferative retinopathy. PPDR: preproliferative retinopathy. PDR: proliferative retinopathy.
SD in parentheses.

*Table 5 Perifoveal intercapillary areas (PIA) and foveal avascular zones (FAZ) and stage of diabetic retinopathy*

| | *No.* | *PIA* *($\mu m^2$)* | *FAZ* *($mm^2$)* |
|---|---|---|---|
| Healthy volunteers | 21 | 3 900 (381) | 0·231 (0·06) |
| NDR | 7 | 6 092 (0176) | 0·276 (0·08) |
| BDR | 17 | 7 119 (1415) | 0·318 (0·18) |
| PPDR | 10 | 8 106 (1782) | 0·513 (0·29) |
| PDR | 14 | 10 990 (3219) | 0·590 (0·31) |
| Significance | | p<0·01 | p<0·05 |

NDR: no retinopathy. BDR: mild to moderate non-proliferative retinopathy. PPDR: preproliferative retinopathy. PDR: proliferative retinopathy.
SD in parentheses.

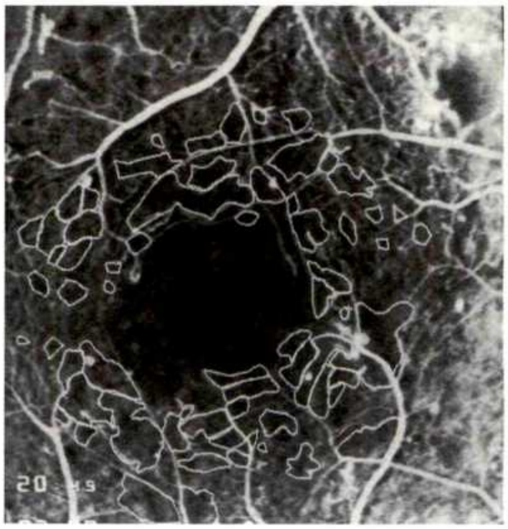

*Figure 5 Interactively marked perifoveal intercapillary areas. These zones show an enlargement compared with those of the patient with mild retinopathy (Fig 2).*

### STATISTICS

The mean value and standard deviation are given for all samples. To assess the significance of the results non-parametric tests were used. For multiple group test statistics the Kruskal-Wallis test with following sequential rejective multiple test procedure[7] was used. Findings with an error probability value less than 0·05 were considered to be statistically significant.

## Results

The clinical and demographic data of the apparently healthy and diabetic subjects are presented in Table 1. The microcirculatory parameters (Tables 2 and 3) in diabetics were compared with reference data of controls published elsewhere.[6] The capillary blood flow velocity (v) in the retinal capillaries of diabetics was significantly (p<0·01; U test) reduced compared with normal subjects.

The coefficient of variation of the capillary blood flow velocity (homogeneity index) of the capillary blood flow velocities showed no signifi-

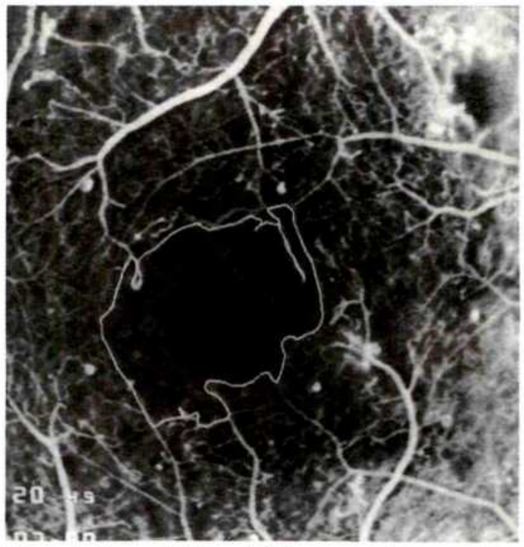

*Figure 6 Interactively marked foveal avascular zone. This is larger than in the patient with mild retinopathy (Fig 3). The normal arcade round the fovea is destroyed.*

*Table 6 Statistical significant differences of perifoveal intercapillary areas (PIA) and foveal avascular zones (FAZ) between the four stages of retinopathy and the healthy subjects*

| *PIA* | | | | | | *FAZ* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *HS* | *NDR* | *BDR* | *PPDR* | *PDR* | | *HS* | *NDR* | *BDR* | *PPDR* | *PDR* |
| HS | – | 0·01 | 0·01 | 0·01 | 0·01 | HS | – | NS | 0·05 | 0 05 | 0·01 |
| NDR | | – | NS | NS | 0·01 | NDR | | – | NS | NS | NS |
| BDR | | | – | NS | 0·05 | BDR | | | – | NS | 0·05 |
| PPDR | | | | – | NS | PPDR | | | | – | NS |
| PDR | | | | | – | PDR | | | | | – |

HS. healthy subjects NDR: no retinopathy. BDR: mild to moderate non-proliferative retinopathy. PPDR. preproliferative retinopathy. PDR: proliferative retinopathy.NS. not significant

cant differences between diabetic and normal subjects (Table 2). The mean area of perifoveal intercapillary areas was more than doubled and the foveal avascular zone was significantly enlarged in the diabetic patients as compared with healthy subjects (Table 3).

Table 4 shows the mean capillary blood flow velocity in perifoveal capillaries of the eyes studied, graded by retinopathy level. There was a slight but not significant decrease in the capillary blood flow velocity with more severe retinopathy level. All subgroups showed a significant ($p<0{\cdot}05$) reduction of flow velocities as compared with the healthy volunteers. No significant differences of the homogeneity index were observed.

Table 5 shows the morphological data for the four subgroups of diabetic patients. The perifoveal intercapillary areas and the foveal avascular zones were significantly different in the four groups. Both parameters enlarged according to the retinopathy level. The mean area of perifoveal intercapillary areas was significantly (two-group statistics) enlarged in all subgroups as compared with the healthy volunteers. Only patients with any diabetic retinopathy (BDR; PPDR; PDR) showed a significant (two group statistics) enlargement of the foveal avascular zone as compared with the healthy subjects.

Table 6 shows the significant levels between the subgroups of diabetic patients and the healthy subjects.

## Discussion

Different techniques have been used to evaluate retinal blood flow in diabetes mellitus.[1-14] The results of this study showed a significant decrease in retinal capillary blood flow velocity in patients with diabetes mellitus compared with normal subjects. This confirms the findings of previous studies,[10 11 15 16] which showed increased arteriovenous passage times in video fluorescein angiograms as a result of a decrease of flow velocities.

The capillary blood flow velocity in perifoveal capillaries showed a slight but not significant decrease at more severe retinopathy levels. Grunwald *et al* found reduced blood flow velocities in eyes with no, mild, or proliferative retinopathy by means of laser Doppler velocimetry.[12] Bertram *et al* showed a significantly decreased mean dye velocity and increased arteriovenous passage times with more severe diabetic retinopathy.[10] Other investigators presented different tendencies of blood flow velocities in more severe diabetic retinopathy. They found a decrease or increase in blood flow velocity, but most can confirm a decrease in blood flow velocities in proliferative retinopathy.[9 14 17-21]

The reduction in capillary blood flow velocity in patients with diabetes mellitus may be due to morphological changes of the vascular bed[22] in combination with the missing capability of vascular autoregulation[23 24] and the decrease of blood fluidity.[25] In particular the influence of plasma viscosity seems to be important for the microcirculation in diabetes mellitus.[26] A reduction in capillary blood flow velocities in diabetes mellitus, too, was observed in the conjunctiva bulbi[16] and the nailfold.[27]

The blood flow velocity in perifoveal capillaries is much higher than in cutaneous[28-30] or conjunctival capillaries.[31 32] This may be due to the high metabolic rate of the retinal tissue. The coefficient of variation of capillary blood flow velocity showed no significant differences between the healthy subjects and the patients with diabetes mellitus and with more severe retinopathy level. This indicates that there is no increase of inhomogeneity in blood flow velocities in patients with diabetic retinopathy and with more severe stages of retinopathy. The reduction of capillary blood flow velocity in diabetics and an unchanged homogeneity index may indicate chronic disturbances of the entire microcirculation in the retinal tissue.

The intercapillary areas are of great importance for the metabolic supply of the retinal tissue. Increasing values of capillary free zones result in increased $O_2$ diffusion time and may cause chronic hypoxia. Lübbers[33] discussed a reduction of oxygen supply in diabetics which is caused by conditions such as reduced red blood cell velocity, narrowing of capillary vessel diameters, and decrease in density of capillary vessels, which is identical with prolonged $O_2$ diffusion length.

In this study patients with diabetes mellitus showed a significant extension of intercapillary areas compared with healthy volunteers; even in patients with no retinopathy an enlargement of the intercapillary areas by about 60% was found. With increasing severity of diabetic retinopathy the intercapillary areas nearly doubled. That the perifoveal capillaries are actually occluded is supported by correlative histopathological studies, in which the capillaries in the non-perfused zone appear as acellular strands.[34 35] Angiographically Sleightholm *et al*[36] and Bresnick *et al*[37] described vascular closure in perifoveal capillaries and increased perifoveal non-perfusion areas in more severe stages of diabetes mellitus.

In agreement with other authors[37-39] we found a significant increase in the mean areas of foveal avascular zones in diabetics as compared with normal subjects. The foveal avascular zones in diabetic patients differ by 40% compared with healthy subjects. With more severe changes in diabetic retinopathy the values rise about 115%. In agreement with other investigators[37 40] we found a significant enlargement of FAZ in progressive diabetic retinopathy.

In conclusion, we found a reduction in capillary blood flow velocities in diabetic patients. In particular, the reduction of flow velocities in patients with no retinopathy indicates that changes of the retinal blood flow are prior to more severe morphological changes. With more severe retinopathy only a slight reduction in capillary blood flow velocities was observed. The quality of glycaemic control (glycosylated haemoglobin: HbAlc) showed no significant differences between the stages of retinopathy evaluated in this study (Table 1).

Histological studies showed that microaneurysm formation, loss of intramural pericytes, and acellular (non-perfused) capillaries are the earliest detectable morphological changes.[34 35] The sequence of these abnormalities is not clear. In this study the perifoveal intercapillary areas showed a marked increase in diabetic patients, even in those with no retinopathy. It can be concluded that capillary closure appears to precede microaneurysm formation in diabetic patients. Depending on the stage of diabetic retinopathy, the perifoveal intercapillary areas and the foveal avascular zones increase significantly. The reduction of capillary blood flow velocities and the increased diffusion times may lead to chronic hypoxia of the retinal tissue. This chronic hypoxia is suspected to be the cause of capillary leakage and neovascularisation.

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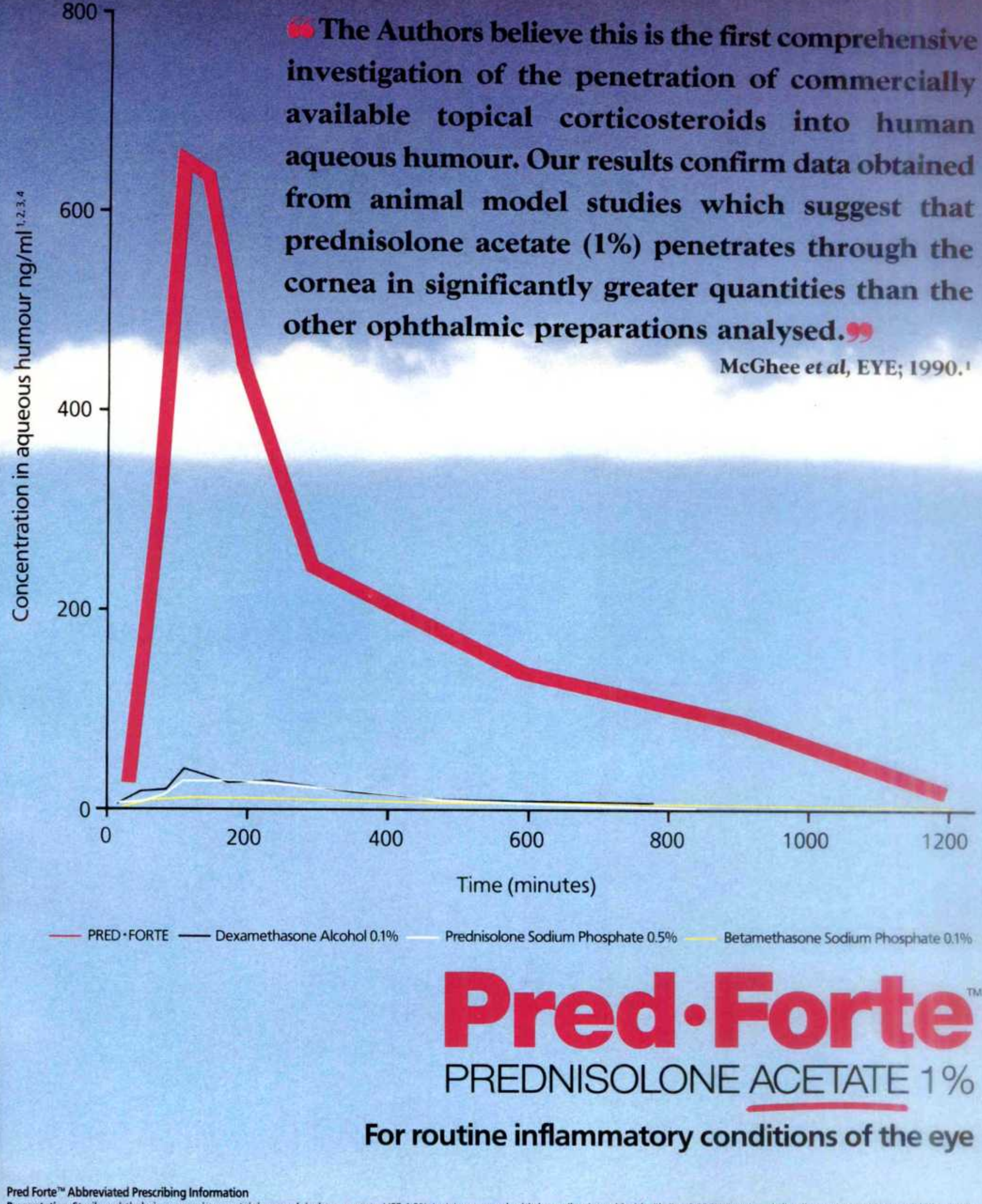

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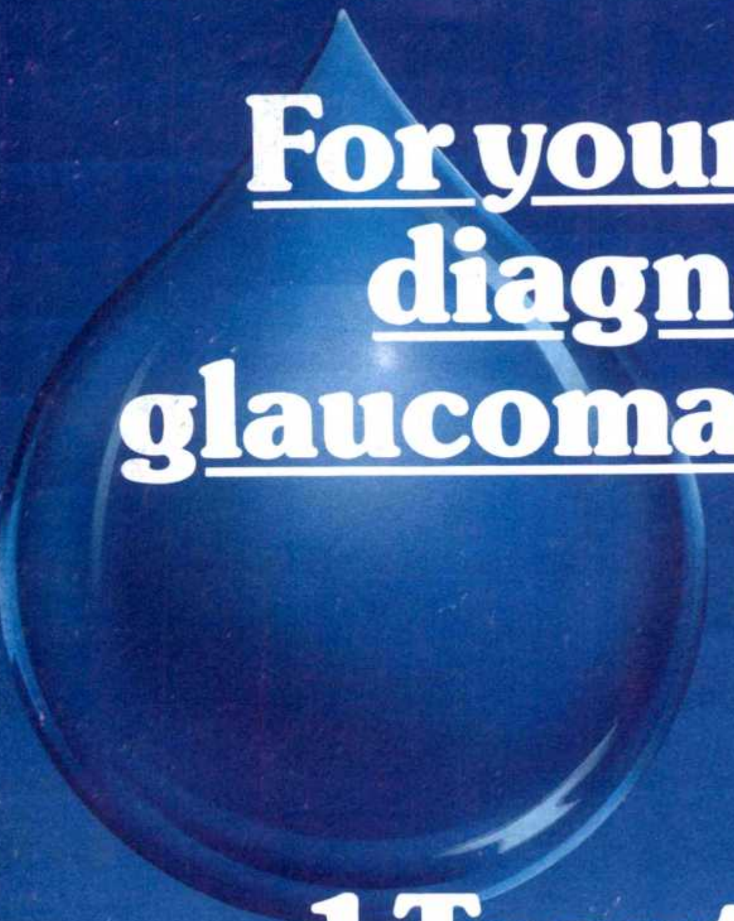

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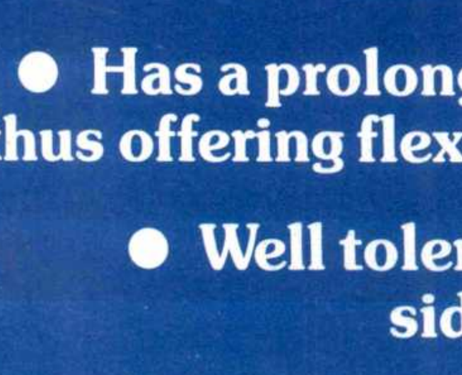

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British Journal of Ophthalmology, 1991, 75, 519–523

# Metipranolol-associated granulomatous anterior uveitis

Tayo Akingbehin, Jose R Villada

## Abstract

**This paper presents for the first time documented evidence, clinical details, and photographic illustrations, of metipranolol-associated granulomatous anterior uveitis in 26 eyes of 15 patients being treated for glaucoma. There were 56 episodes of granulomatous anterior uveitis, all associated with large (mutton-fat) keratic precipitates, flare, cells, and 'white eyes' (except in seven episodes). In 30 (53·6%) of these episodes there was loss of control of intraocular pressure. Metipranolol 0·6% was implicated in 54 of the 56 episodes and metipranolol 0·3% in the remaining two. Fifty-one other cases of metipranolol-associated granulomatous anterior uveitis have so far been reported from other parts of the country to the Committee on Safety of Medicines. As a result multidose metipranolol in 0·1%, 0·3%, and 0·6% strengths has been withdrawn from clinical use in the United Kingdom. The pathogenesis of this adverse drug reaction is uncertain.**

The use of β-blockers as topical ophthalmic preparations to reduce the intraocular pressure marked the start of a new era in the medical management of glaucoma, because of their efficacy, prolonged therapeutic action, and few serious systemic and ocular adverse effects.[1,2] As a result they became the first choice for the medical treatment of glaucoma. However, in recent years the increasing number of systemic and ocular adverse effects have led to their more cautious use despite the development of newer drugs with supposedly fewer side effects.[3]

In the United Kingdom there are five β-blockers available as ophthalmic topical preparations approved for clinical use, namely, betaxolol, carteolol, levobunolol, metipranolol (now withdrawn), and timolol. Metipranolol (1,-(4 acetoxy-2,3,5-trimethylphenyloxy)-3-isopropylacyno-propan-2-ol) was introduced in the UK in 1986 with the proprietary name of Glauline and available in three strengths: 0·1%, 0·3%, and 0·6%. It is a non-selective β-blocker with no intrinsic sympathomimetic or membrane stabilising properties and only slight local anaesthetic activity.[4]

The efficacy of metipranolol in lowering intraocular pressure has been reported in several studies,[5-9] and so have the adverse effects, which are similar to those of other ophthalmic topical β-blockers. The ocular adverse effects attributed to metipranolol have included: subjectively, burning or stinging on instillation, eye pain or uncomfortable dryness, foreign body sensation, itching, blurred vision; objectively, allergic blepharoconjunctivitis, conjunctival hyperaemia, punctate keratopathy, corneal anaesthesia, and dry eye syndrome.[10] It has been suggested that metipranolol is less tolerated than the other β-blockers because of the stinging and burning sensation on instillation.[7,11]

This paper documents for the first time case histories of some patients receiving this drug for the treatment of glaucoma who developed granulomatous anterior uveitis. The clinical details are reviewed briefly, and photographic evidence submitted. The clinical presentation and behaviour of the affected eyes are analysed.

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## Methods and materials

At the beginning of 1990 a cluster of cases of severe metipranolol-associated blepharoconjunctivitis focused attention on this drug. The reaction was more severe than usually seen and two patients (three eyes) had coincidental granulomatous anterior uveitis. The bottles of metipranolol were collected from all the patients who suffered from both forms of adverse reactions and their batch numbers identified. There was no consistency in the batch numbers to suggest faulty preparation or contamination of the drug. During this inquiry six more patients were identified in the clinics and ophthalmic ward with granulomatous anterior uveitis while being treated with metipranolol for glaucoma. There were now eight patients, 15 eyes, with granulomatous anterior uveitis, all receiving metipranolol and no other common denominator.

In view of these findings we decided to review the case notes of all the patients in the department using metipranolol in any of its three strengths. The patients were identified through the Drug Register in the Pharmacy Department, the records from January 1989 to March 1990 being examined. All the patients on metipranolol 0·6% were then invited for an ocular examination.

## Results

Two hundred and forty-seven case notes of patients treated with metipranolol in all strengths were reviewed. There were 109 case notes of patients using metipranolol 0·6% and 76 patients from this group attended special metipranolol clinics for examination. Eleven patients had active granulomatous anterior uveitis when seen in either special or normal clinics, and four had had attacks, well documented in the case notes, but had quiet eyes when examined. In total there were 15 patients (13·8% of the patients on metipranolol 0·6%) with presumed metipranolol-associated granulomatous anterior uveitis, 11 of these with bilateral attacks and four with unilateral, making a total of 26 eyes. All

*Table 1* *Clinical details of patients with metipranolol-associated granulomatous anterior uveitis*

| Case | Sex | Age | Eyes involved | Dose of metipr | No of episodes | Other eyedrops | Ocular surgery |
|---|---|---|---|---|---|---|---|
| 1 | F | 87 | RE | 0·6% | 2 | Dipivefrine | Cataract+IOL |
| | | | LE | 0·6% | 2 | Dipivefrine | Cataract+IOL |
| 2 | F | 76 | RE | 0 6% | 1 | – | – |
| | | | LE | 0 6% | 2 | – | – |
| 3 | F | 70 | RE | 0·6% | 1 | – | Cataract+IOL; trabeculectomy |
| 4 | F | 79 | RE | 0·6% | 1 | Dipivefrine | – |
| 5 | M | 70 | RE | 0·6% | 3 | – | – |
| | | | LE | 0·6% | 3 | – | – |
| 6 | M | 86 | RE | 0 6% | 4 | Adrenaline | – |
| | | | LE | 0·6% | 4 | Adrenaline | – |
| 7 | F | 85 | RE | 0·6% | 1 | – | – |
| | | | LE | 0 6% | 1 | – | – |
| 8 | F | 67 | RE | 0·6% | 1 | Levobunolol | – |
| | | | LE | 0 6% | 1 | Levobunolol | – |
| 9 | M | 76 | RE | 0·6% | 2 | Timolol 0 5% | – |
| | | | LE | 0·6% | 2 | Timolol 0·5% | Cataract+IOL |
| 10 | F | 84 | RE | 0·6% | 1 | Dipivefrine | – |
| | | | LE | 0·6% | 1 | Dipivefrine | – |
| 11 | M | 75 | RE | 0·6% | 3 | – | – |
| | | | LE | 0·3% | 2 | – | – |
| 12 | F | 74 | RE | 0·6% | 3 | – | – |
| | | | LE | 0·6% | 3 | – | – |
| 13 | F | 57 | LE | 0·6% | 1 | – | Trabeculectomy |
| 14 | F | 58 | LE | 0·6% | 2 | Dipivefrine | Retinal detachment; cataract; trabeculectomy |
| 15 | F | 82 | RE | 0·6% | 4 | Pilocarpine 2% | – |
| | | | LE | 0·6% | 5 | Pilocarpine 2% | – |
| | | | 26 | | 56 | | |

these eyes except one developed granulomatous anterior uveitis while being treated with metipranolol 0·6% to both eyes; one patient received metipranolol 0·3% in one eye as shown in Table 1. The table also shows the age/sex distribution of the patients.

Of the 15 patients with metipranolol-associated granulomatous anterior uveitis 11 were females with an age range 57–87 years (mean 74·4 years) and four males, age range 70–86 years (mean 76·7 years). The age range for all the patients was 57–87 years (mean 75 years).

The female to male ratio as 3:1, and the age range and mean age of the 15 patients were all consistent with those of the glaucoma population. Of the 26 eyes affected the right and left were equally involved (13 each), with a similar number of separate episodes of granulomatous anterior uveitis.

There were no systemic or ocular disorders common to these patients. Two of them had diabetes mellitus (one insulin-dependent and the other on oral hypoglycaemics).

Six eyes of five patients had intraocular surgery prior to treatment with metipranolol of any strength and the development of granulomatous anterior uveitis. A total of nine intraocular operations had been performed on the six eyes: cataract surgery (five eyes), trabeculectomy (two eyes), retinal detachment surgery with silicone oil (one eye). One eye (case 14, LE) had retinal detachment surgery, cataract extraction, and trabeculectomy at different times and developed the first episode of granulomatous anterior uveitis at least 15 months after the last operation.

Analysis of the drug history of the 15 patients with metipranolol-associated granulomatous anterior uveitis was unproductive. There was no common factor between the various systemic medications. Thirteen eyes of eight patients were on additional topical ophthalmic medications when they developed granulomatous anterior

*Table 2* *Period on drug before the first episode of granulomatous anterior uveitis and distribution of episodes versus metipranolol dose*

| Drug | No eyes | No episodes | Period on drug befo 1st episode in month | |
|---|---|---|---|---|
| | | | Range | Mean |
| Metipranolol 0·3% | 1 | 2 | | 31 |
| Metipranolol 0·6% | 25 | 54 | 2–24 | 11·72 |
| Total | 26 | 56 | 2–31 | 12·46 |

uveitis: pilocarpine 2% eyedrops (three eyes) dipivefrine 0·1% eyedrops (four eyes), adrena line 1% eyedrops (two eyes), levobunolol 0·5% eyedrops (two eyes), and timolol eyedrops 0·5% (two eyes) (Table 1).

Twenty-six eyes (13 right and 13 left developed uveitis with at least 56 separat documented episodes (27 in the right eye and 2 in the left) over a period of 30 months, from October 1987 to March 1990. Fifty-four episode occurred in 25 eyes treated with metipranol 0·6% and two episodes in one eye treated wit metipranolol 0·3%. The interval between th beginning of the treatment and the first episod of uveitis is shown in Table 2.

Of the 26 eyes identified with uveitis 16 ha further episodes while they remained on th metipranolol drops. The mean interval betwee the first and second episodes in these 16 eyes wa 4·75 months (range 3–9 months). Nine of the 1 eyes had a third episode after a mean interval o 3·6 months (range 1–10 months). Four out of 2 eyes had four episodes each; the interval between the third and fourth episodes range from one to 6 months, mean 2·5 months. Onl one of these eyes developed a fifth episode o uveitis after a period of six months (Tables 3 an 4).

The 56 episodes of granulomatous anterio uveitis were managed in various ways, as sum marised in Table 5.

Brief reports on some of the 15 patients follow

CASE 2

This was a 76-year-old Caucasian female with n relevant past medical history or drug history Her bilateral open angle glaucoma was diagnose in July 1986 and she was started on timol 0·25%. Owing to poor intraocular pressur

*Table 3* *Distribution of episodes of granulomatous anterior uveitis*

| No. of episodes of anterior uveitis | No of eyes | % of total eyes | Cumulative total no of episodes |
|---|---|---|---|
| 1 | 26 | 100 | 26 |
| 2 | 16 | 61 5 | 42 |
| 3 | 9 | 34·5 | 51 |
| 4 | 4 | 15 5 | 55 |
| 5 | 1 | 3·5 | 56 |

*Table 4* *Time interval between episodes in eyes which developed several attacks of granulomatous anterior uveitis*

| Episodes of anterior uveitis | Interval in months | No. of eyes | Range in months | Mean months |
|---|---|---|---|---|
| 1st–2nd | 3,3,3,3,3,9,9,4,4, 3,5,7,7,4,3,6 | 16 | 3–9 | 4·75 |
| 2nd–3rd | 1,1,1,1,4,10,10,2,3 | 9 | 1–10 | 3 60 |
| 3rd–4th | 1,1,6,2 | 4 | 1–6 | 2 50 |
| 4th–5th | 6 | 1 | | |

*Table 5 Management of episodes of granulomatous anterior uveitis*

| *Topical steroid used* | *No. episodes* | *Mydriatics* | *Other glaucoma treatments* | *Average time of resolution (weeks)* |
|---|---|---|---|---|
| Prednisolone 1% | 24 | Atropine 1%×2<br>Cyclopent 1%×2<br>Tropicamide 1%×2 | Acetazolamide×8 | 3·8 |
| Dexamethasone 0·1% | 12 | Cyclopent 1%×4 | Acetazolamide×6 | 2·6 |
| Fluoromethalone 0·1% | 5 | Cyclopent 1%×4 | Acetazolamide×4 | 4·4 |
| Betamethasone 0·1% | 4 | Cyclopent 1%×4 | Acetazolamide×2 | 3·5 |
| Prednisolone 0·5% | 1 | – | – | 1·0 |
| No steroids | 6 | – | – | 6·0 |

In four of the episodes the time of resolution was not clear from the case notes and they are not included in this table.
×2=in two episodes, and likewise for ×4.

(IOP) control her medications were varied until January 1988, when timolol was stopped and she was started on metipranolol 0·6% twice daily to both eyes as the only antiglaucoma treatment. Two years later (January 1990) she developed bilateral anterior uveitis with keratic precipitates and loss of IOP control. This episode was treated with topical steroids (fluorometholone eyedrops), mydriatics, and acetazolamide, and recovered completely in three weeks with return of the IOP to normal. She was recalled to the Special Metipranolol Review Clinic in April 1990 and found to have bilateral blepharoconjunctivitis, left anterior uveitis with keratic precipitates, and loss of IOP control in both eyes. The left eye was photographed (Fig 1). This second episode was not treated with topical steroids, the metipranolol 0·6% was stopped, and she was started on carteolol 2% twice daily to both eyes. Two weeks later both eyes were white and quiet, the keratic precipitates old, and IOPs within normal limits.

### CASE 6

This was an 86-year-old Caucasian man who suffered from gastrointestinal haemorrhage and secondary anaemia treated with ferrous sulphate tablets. Glaucoma was diagnosed in about 1983. The first record of treatment with metipranolol 0·6% was in September 1987; in addition he received adrenaline 1% twice daily to both eyes. He developed bilateral anterior uveitis with keratic precipitates and posterior synechiae in April 1989. He was treated as a case of bilateral Fuchs's cyclitis at another hospital and registered fully blind. Later he was transferred to a rest home in Southport and an ophthalmic opinion was requested. At this time he had bilateral anterior uveitis with mutton-fat keratic precipitates, posterior synechiae (Fig 2), and uncontrolled IOPs. The possibility of metipranolol-associated uveitis was being investigated, hence the metipranolol was discontinued, and he was started on timolol 0·5% and treated with eyedrops of prednisolone acetate, and atropine 1%. The condition resolved in two months. The visual acuity improved from hand movements in both eyes when was registered blind to 6/12 RE and 6/36 LE. The IOPs were controlled with timolol 0·25%.

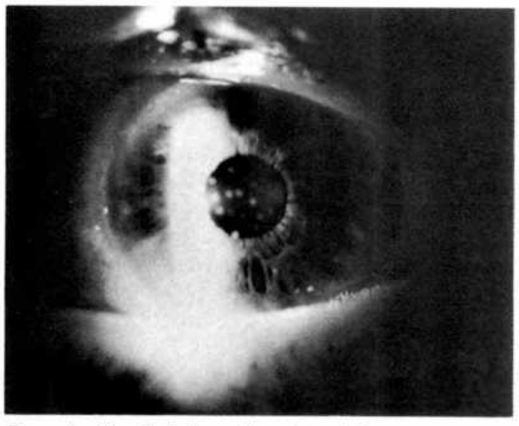

*Figure 1 Case 2. Left eye: keratic precipitates.*

### CASE 9

This was a 76-year-old Caucasian male with no relevant medical history. He was diagnosed as suffering from bilateral cataracts and open angle glaucoma in December 1987, and was started on treatment with metipranolol 0·3% twice daily to both eyes. He underwent left cataract extraction with IOL in January 1988, and the IOPs remained stable without treatment for six months. The pressures then rose in both eyes and led to gradually increasing treatment, eventually to metipranolol 0·6% and timolol 0·5% twice daily to both eyes in March 1989. The first episode of bilateral anterior uveitis with keratic precipitates was in November 1989; it was treated with topical steroids (prednisolone acetate), and recovered in three weeks. The second episode with fresh keratic precipitates and loss of IOP control occurred in March 1990 (both eyes photographed, Figs 3 and 4) and led to the metipranolol drops being changed to timolol 0·5% twice daily to both eyes. This episode was not treated with steroids. He had a slower recovery but with complete resolution in eight weeks.

### CASE 10

This was an 84-year-old diabetic woman on oral hypoglycaemic treatment and also being treated for systemic hypertension and arthritis. She had bilateral open angle glaucoma which needed increasing treatment, and her first contact with metipranolol 0·6% was in April 1989. She was listed for filtration surgery in December 1989, and at that time her treatment was metipranolol 0·6% twice daily and dipivefrine 0·1% twice daily to both eyes. When admitted for surgery, in February 1990, she was found to have bilateral anterior uveitis with mutton-fat keratic precipi-

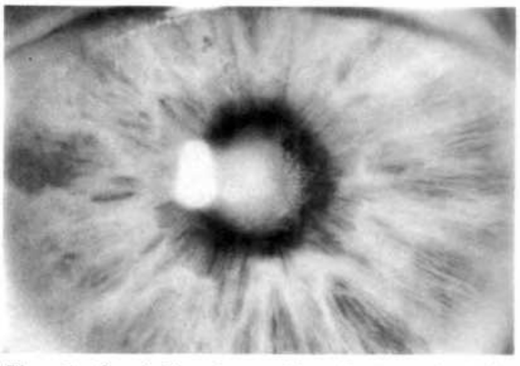

*Figure 2 Case 6. Posterior synechiae after repeated episodes of anterior uveitis.*

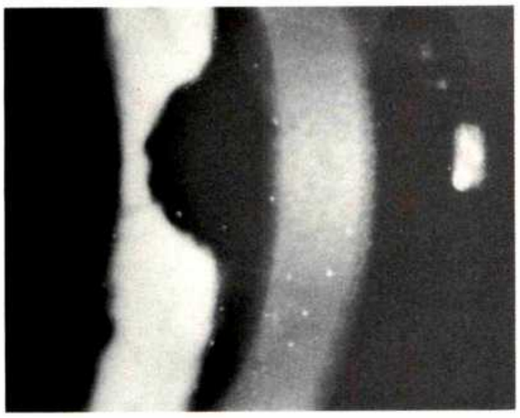

*Figure 3 Case 9. Right eye: keratic precipitates.*

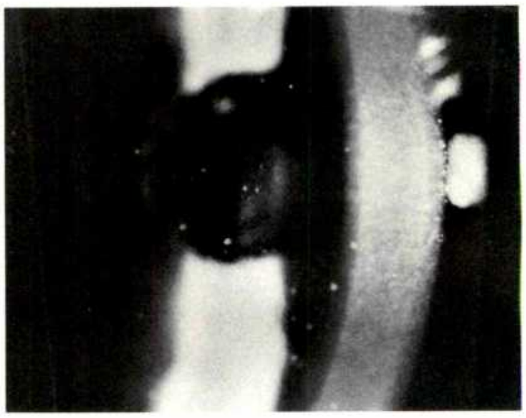

*Figure 4 Case 9. Left eye: keratic precipitates.*

tates and very elevated IOPs (62 mm Hg in the right eye and 66 mm Hg in the left). There were no positive radiological or biochemical findings and she was treated with topical steroids (prednisolone acetate). The metipranolol was changed to timolol 0·5% twice daily, and acetazolamide. She continued with the dipivefrine 0·1% The uveitis recovered in three weeks with normal intraocular pressures on the above treatment until bilateral trabeculectomy.

CASE 11

This was a 75-year-old Caucasian man suffering from angina and pernicious anaemia. He was diagnosed as having open angle glaucoma first in the right eye and two years later in the left. In February 1989 his treatment was increased to metipranolol 0·6% to the right eye and metipranolol 0·3% to the left eye. He developed right anterior uveitis with keratic precipitates and loss of pressure control seven months later (September 1989). This eye was treated with dexamethasone-hypromellose eyedrops, with full recovery from the uveitis and return to normal of the IOP. Three months later (December 1989) he developed bilateral anterior uveitis with keratic precipitates; both eyes were treated with prednisone eyedrops, with full recovery. He had a third episode of bilateral blepharoconjunctivitis, bilateral anterior uveitis with keratic precipitates, loss of pressure control, and right ectropion secondary to the skin changes. The metipranolol drops were stopped, he was started on timolol 0·25% twice daily to both eyes, and both eyes were treated with prednisolone eyedrops. The ectropion and the ocular inflammation resolved in six weeks.

## Discussion

Almost all the ocular adverse effects of the ophthalmic topical β-blockers reported to date have affected adnexal or external ocular structures and are thought to be related to their property of membrane stabilisation or to reflect the different vehicles, the pH, and concentrations of the drugs.[10] Metipranolol is known to produce external ocular inflammatory reactions which include periorbital dermatitis, urticaria, blepharitis, blepharoconjunctivitis, keratitis and 'eye pain' (Committee on Safety of Medicines, personal communication). There has also been a case report of metipranolol-associated conjunctivitis with epithelial keratinisation, similar to the conjunctival reaction seen after oral use of practolol.[12] We have documented a case of bilateral marginal keratitis associated with metipranolol 0·3%.

This paper presents the first documented reports of ophthalmic topical β-blocker-associated intraocular inflammation. In 1980 Van Buskirk[13] reviewed 547 reports of adverse reactions to timolol maleate received by the American National Registry for Drug induced ocular side effects and found six cases of uveitis associated with the use of timolol in an 11-month period. No details were available. Three years later Zimmermann *et al*[14] updated the review of the American National Registry of Drug induced ocular side effects of timolol, and the number of associated cases of uveitis had increased to 14, but no details were given. To put this in perspective, they also found 98 cases of ocular irritation, 64 cases of blepharoconjunctivitis, 38 cases of keratitis, and 29 cases of 'corneal lesions' due to timolol from 1472 case reports. No cause-and-effect relationship was implied or demonstrated for any of these reported reactions.

This paper presents evidence for metipranolol-induced granulomatous anterior uveitis in 15 patients, with 26 eyes affected. We are also aware of 51 patients, at the time of submitting this paper, from other parts of the country with suspected metipranolol-induced anterior uveitis (Committee on Safety of Medicines, personal communication). In this study 25 affected eyes were receiving metipranolol 0·6%, and one eye metipranolol 0·3%. By comparing the number of cases reported with sales figures for metipranolol 0·6% and metipranolol 0·3% in the UK we believe the incidence of metipranolol-associated anterior uveitis is about 3·8 per thousand for metipranolol 0·6%, 1·13 per thousand for metipranolol 0·3%, and 0·5 per thousand for metipranolol 0·1% (Smith and Nephew Pharmaceuticals Ltd, personal communication). These figures appear to be increasing with greater awareness of this adverse drug reaction.

Granulomatous anterior uveitis is characterised by a tendency to form iris nodules (Koeppe or Busacca type) and mutton-fat keratic precipitates. Non-granulomatous anterior uveitis has little or no tendency to form either nodules or mutton-fat keratic precipitates.[15] All 26 eyes affected had keratic precipitates on the first and subsequent attacks of anterior uveitis. The attacks of granulomatous anterior uveitis recorded in the case notes before the establishment of the Special Metipranolol Clinics recorded mutton-fat keratic precipitates in about 50% of the episodes and diagramatically showed large keratic precipitates in the other 50%. All the cases of active uveitis found by chance at the beginning of this investigation and during the recall examinations had mutton-fat keratic precipitates. The keratic precipitates seen by the investigators were white initially, with no particular pattern to their distribution on the corneal endothelium. No episode of anterior uveitis was associated with Koeppe or Busacca type nodules.

All 56 episodes of anterior uveitis in the 26 eyes were therefore characterised by keratic precipitates, flare, and cells in the anterior chamber. Most of the eyes were described as 'white' when the diagnosis of anterior uveitis was made, but seven episodes had coexisting significant blepharoconjunctivitis. Three eyes developed posterior synechiae. In 30 out of the 56 attacks of granulomatous anterior uveitis (53·8%) the IOP was raised, and additional therapy was required to control the pressure in most of them. Acetazolamide was used on every occasion (Table 5). The IOP of eyes with metipranolol associated side effects is the subject of a separate investigation.

All but six episodes of anterior uveitis were treated with topical steroids (Table 5). The average resolution period of the anterior uveitis when treated ranged from 2·6 to 4·4 weeks, but in the six eyes which received no topical steroids and were treated only by discontinuation of the metipranolol drops the average time for recovery was longer at six weeks. This difference was statistically significant ($p<0{\cdot}0125$). A mydriatic was used in combination with topical steroids in treating 18 episodes of granulomatous anterior uveitis. The eyes recovered fully without any sequelae except for the three eyes which developed posterior synechiae. The IOP in the eyes which required additional glaucoma therapy returned to preuveitic levels on recovery and did not need the continuation of the additional therapy. When metipranolol was discontinued, the IOP was controlled easily with an alternative therapy.

All the 26 eyes have now been followed up for a minimum period of 10 months following the discontinuation of metipranolol. None of the eyes has shown any evidence of further intraocular inflammation with the substituted antiglaucoma therapy, which includes other commonly used ophthalmic topical β-blockers.

In conclusion, this paper presents clinical and photographic evidence for the first time of a hitherto unreported adverse association between metipranolol therapy and granulomatous anterior uveitis. As a result of reporting these cases to the Committee on Safety of Medicines and to Smith and Nephew Pharmaceuticals Ltd a letter was written by Smith and Nephew to all ophthalmologists in the UK on 2 April 1990 to advise them on the possible association of metipranolol 0·6% with granulomatous anterior uveitis. A subsequent communication to all ophthalmologists, general practitioners, and pharmacists on 3 August 1990 from Smith and Nephew announced the withdrawal of metipranolol 0·6% from the UK market as from 1 October. The 0·1% and 0·3% strengths of metipranolol continued to be available for prescription for another six months. After further reports of metripranolol-associated granulomatous anterior uveitis (the latest figures being: 48 patients on metipranolol 0·6%, 17 on 0·3%, and 1 on 0·1% – Committee on Safety on Medicines, personal communication) Smith and Nephew wrote again, on 4 January 1991, to all ophthalmologists announcing the withdrawal from the market of the remaining two strengths of metipranolol 0·1% and 0·3%. This drug is still available for prescription in the single disposable form. The pathogenesis of these adverse reactions remains uncertain but is being investigated.

Our thanks to Sister Anne E Lewis for help in carrying out this study, and to Miss Sharon A A McGowan and Mrs Elizabeth Warrington for secretarial assistance

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# Ocular manifestations in fetal alcohol syndrome

T Chan, R Bowell, M O'Keefe, B Lanigan

**Abstract**

**Eight children with the fetal alcohol syndrome are described with ocular anomalies. They all had a strong history of maternal alcohol abuse throughout pregnancy, especially in the first trimester. All the children had eye abnormalities. These included external eye lesions, Peters' anomaly, lens opacification, ocular motility disorders, and optic nerve hypoplasia.**

Fetal alcohol syndrome is characterised by at least three of the following findings: (1) marked pre- and postnatal growth deficiency with generalised dystrophy (weight, length, and/or head circumference below the 10th percentile when corrected for gestational age); (2) involvement of central nervous sytem (signs of neurological abnormality,[1] intellectual impairment, or developmental delay); (3) typical facies with at least two of the following signs: microcephaly (head circumference below the third percentile), microphthalmia and/or short palpebral fissures, long philtrum, thin upper lip, and flattening of the maxillary area.[2] Supplementary findings such as skeletal, cardiac, or genitourinary anomalies are also common. A wide variety of abnormalities during embryogenesis may result in a spectrum of change from minor alteration to the full blown syndrome.

We describe eight children, four males and four females, presenting at age 1 month to 6 years. All had a strong maternal history of alcohol abuse during pregnancy.

## Case reports

### CASE 1

A 1-month-old boy presented with a history of severe maternal alcohol abuse and the dysmorphic features of fetal alcohol syndrome. Chromosomal analysis and screening for intrauterine infection gave negative results. Ophthalmic examination revealed bilateral ptosis, short palpebral fissures, telecanthus, microphthalmia, bilateral Peters' anomalies (left more severe than right), nystagmoid eye movements, bilateral peripheral anterior synechiae, and partial obliteration of anterior chambers. The intraocular pressures and corneal diameters were normal. An ultrasound B scan showed normal posterior segments; the visual evoked response and binocular electroretinogram were normal.

A 7 mm full-thickness corneal graft was performed at the age of 4 months on the right eye. Follow-up showed slight anterior subcapsular cataract inferiorly in the right eye at 9 months. The corneal graft remains clear to date with a myopic fundus. Microscopic examination of the corneal button showed epithelial oedema with extensive destruction of Bowman's layer and superficial stromal fibrosis. Descemet's membrane and endothelial cells were distinguished only at the edges of the specimen. Posterior corneal surface elsewhere showed keratocyte proliferation and absence of Descemet's membrane associated with fibrous strands with corneal adhesions.

### CASE 2

A 1-year-old girl presented with failure to thrive since birth and a history of maternal alcohol abuse. Investigations for intrauterine infection and chromosomal studies gave normal results. Examination showed growth and developmental delay, and on ophthalmic examination she had central steady fixation bilaterally, a left ptosis (2 mm), and a small esotropia. Cycloplegic refraction was +3·0 dioptres sphere (DS) in both eyes and the fundi were normal.

### CASE 3

A 4-month-old boy with a history of maternal alcohol abuse was born at 35 weeks gestation with a birth weight of 1·6 kg. He had developmental delay.

Ophthalmic examination revealed fixation bilaterally. He also had a horizontal jerk type of nystagmus of moderate amplitude and frequency in all directions of gaze. Funduscopic examination showed bilateral optic nerve hypoplasia, marked peripapillary depigmentation and peripheral pigmentary clumping, with surrounding chorioretinal atrophy. The electroretinogram was normal, but the visual evoked response was abnormal. At the age of 2 years he fixed and followed but developed an abnormal head posture. Cycloplegic refraction was +3·5 DS bilaterally.

### CASE 4

A 2-month-old baby girl with a history of maternal alcohol abuse was referred after her recovery from a hypoxic episode and treated with anticonvulsants for posthypoxic seizures. She had a history of developmental delay, a duplex collecting system, and hydronephrosis of the left renal system.

Ophthalmic examination showed broad epicanthus, short palpebral fissures, and central steady fixation. Funduscopic examination showed bilateral optic nerve hypoplasia.

### CASE 5

A 6-month-old boy was born at 41 weeks gestation with meconium grade 3. He had a marked bradycephaly, developmental delay, a right congenital dislocation of hip, and an inguinal

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*Table 1 Systemic features of patients with fetal alcohol syndrome*

| Case | History of alcohol | Typical FAS features | Growth delay | Mental retardation | Skeletal deformities | Other |
|---|---|---|---|---|---|---|
| 1 | + | + | + | + | + | ASD, undescended testes, gastroesophageal and vesicoureteric reflux |
| 2 | + | + | + | + | 0 | |
| 3 | + | + | + | + | 0 | |
| 4 | + | + | + | + | 0 | Duplex collecting system and hydronephrosis; neonatal irritability; posthypoxic seizures |
| 5 | + | + | + | + | + | Inguinal hernia; partial absence of corpus callosum |
| 6 | + | + | + | + | + | |
| 7 | + | + | + | + | 0 | Cerebral palsy; neonatal jaundice; cerebral atrophy; ventricular dilatation |
| 8 | + | + | + | 0 | + | |

Present +; Absent 0; Unknown –. ASD=atrial Septal defect.

hernia. Ultrasound examination showed a partial absence of the corpus callosum. Ophthalmic examination showed antimongoloid slants and short palpebral fissures, with a 2 mm left ptosis. He had a long philtrum and thin upper lip. Funduscopy showed bilateral optic nerve hypoplasia, and cycloplegic refraction was +4·0 DS both sides. Electrodiagnostic tests were carried out, including visual evoked response, which showed small amplitudes; the electroretinogram was normal.

### CASE 6

A 6-year-old girl presented with a history of developmental delay, recurrent respiratory infections, and dysmorphic facies.

She had a left esotropia, and at follow-up at one year after strabismus surgery she still had a small residual left esotropia. Cycloplegic refraction showed +4·50/+1·0 cylinder at 80° in the right eye and +4·5 DS in the left. Funduscopic examination showed normal appearances.

### CASE 7

A 9-month-old baby girl was born at 34 weeks gestation with a history of maternal alcohol abuse after spontaneous rupture of membranes and a birth weight of 1·8 kg. On physical examination she had signs of a mixed dystonic and spastic type of cerebral palsy. Ultrasound scan of the brain showed cerebral atrophy and lateral ventricular dilatation. Computerised tomography showed diffuse atrophic changes of the brain, ventricular enlargement, and small brainstem.

She had wandering eye movements, and funduscopy showed bilateral optic nerve hypoplasia. The visual evoked response showed low amplitude and prolonged latency; the electroretinogram was normal.

### CASE 8

A 2-year-old boy with a history of maternal alcohol abuse during pregnancy presented with bilateral partial ptosis (moderate levator function) and bilateral antimongoloid slant. Funduscopy showed bilateral tortuosity of retinal vessels. Cycloplegic refraction showed +0·5 DS/+1·0 dioptre cylinder (DC) at 110° of the right eye and +2·5 DC at 60° of the left eye. He then had the Fansanella Servat procedure for the correction of the left ptosis.

## Discussion

The incidence of the fetal alcohol syndrome is 1:750 in the USA[3] and 1:600 in Sweden.[4] Affected children are usually mentally retarded and prone to frequent infections, failure to thrive, and may need operative correction for various skeletal, cardiac, or genitourinary defects.

The teratogenic effects of alcohol on ocular embryogenesis are multiple. Although the exact mechanism is unknown, it could be directly related to ethyl alcohol or its metabolite, acetaldehyde, or to secondary deficiencies. The developmental anomalies present a wide spectrum of severity involving the external eye, anterior segment, and posterior pole. Miller *et al*[5] reported eight cases of anterior segment anomalies associated with the syndrome. Seven of them had Peters' anomaly and one had Axenfeld's

*Table 2 Ocular anomalies in patients with fetal alcohol syndrome*

| Case | External eye | Anterior segment abnormality | Motility | Fundus | Refraction | Visual acuity |
|---|---|---|---|---|---|---|
| 1 | Short palpebral fissure, telecanthus, ptosis | Peters' anomaly, peripheral anterior synechiae | Exotropia OS | Myopic OD | OD –3·0 | 6/36 to 6/60 |
| 2 | Ptosis | 0 | Esotropia OS | 0 | OD +3·0 | Fix +<br>Fix + |
| 3 | 0 | 0 | Horizontal type nystagmus | Optic nerve hypoplasia, chorioretinal atrophy | OD –3·5<br>OS –3·5 | Fix +<br>Fix + |
| 4 | Epicanthus, short palpebral fissure | 0 | 0 | Optic nerve hypoplasia | — | Fix +<br>Fix + |
| 5 | Antimongoloid slants, ptosis, short palpebral fissure | 0 | 0 | Optic nerve hypoplasia | OD +4·0<br>OS +4·0 | Fix +<br>Fix + |
| 6 | 0 | 0 | Esotropia OS | 0 | OD +4·5/+1·0 DC at 80°<br>OS +4·5 | OD 6/6<br>OS 6/9 |
| 7 | 0 | 0 | Wandering eye movement | Optic nerve hypoplasia | — | |
| 8 | Ptosis | 0 | 0 | 0 | OD +0·5/+1·0 DC at 110°<br>OS +2·5 DC at 60° | OD 6/9<br>OS 6/12 |

Present +. Absent 0. Unknown –. Fix + = fixation is present.

anomaly. There was one case with tortuosity of retinal vessels.

Embryologically a normal endothelium is essential for the secretion of Descemet's membrane, which begins at about 12–14 weeks gestation. If the teratogenic effect of alcohol occurs before the initial mesenchyme migration to form the corneal endothelium, keratocytes and iris stromal cells (about six weeks gestation), the endothelium, and Descemet's membrane might reach only the peripheral cornea.[5]

Stromland[6] in a review of ocular abnomalies in 30 cases reported that 48% of the eyes showed hypoplasia of the optic nerve head and 49% had abnormal tortuosity of the retinal arteries. However, only 10% had anterior segment and media abnormalities (microcornea, cataract, iris defects, and persistent hyaloid artery), and none of them had either Peters' or Axenfeld's anomaly. He concluded that the teratogenic effects of alcohol on the developing optic nerve is from the appearance of the first retinal ganglion cell in the sixth gestational week until after birth. Retinal vascularisation takes place from the 16th gestational week until delivery at term. He suggested that the combination of tortuosity of retinal vessels and optic nerve hypoplasia are helpful signs for the diagnosis of the fetal alcohol syndrome.[6-8] This is supported from the findings of Provis *et al*[9] who reported that the development of mature ganglion cells appears to coincide with retinal vascularisation.

The degree of teratogenicity of an agent suggested by Wilson[10] depends mainly on three factors. First is the genotype of the embryo and its interaction with environmental factors. This could explain the wide variety of lesions in this syndrome shown in the studies reported by Miller *et al*,[5] Stromland,[6] and ourselves. All the cases reported by Miller *et al*[5] had mainly anterior segment anomalies, and the majority of the patients were from the black population. Stromland[6] reported chiefly posterior segment anomalies, and most of the children reported were Caucasian (Swedish) in origin. In our study the findings are more comparable with those of Stromland, with four (50%) cases of hypoplasia of the optic nerve, one with Peters', anomaly and one case of tortuosity of retinal vessels. A genetic factor may cause a different degree of susceptibility to ocular embryogenesis.

Secondly, a factor to consider is the susceptibility of toxic agents, which depends on the timing of insult during embryogenesis. This would partly explain the various abnormalities mentioned earlier in the anterior segment and posterior pole. A 'critical period' in gestation when alcohol would have its most pronounced teratogenic effects on different parts of the growing eye could not be identified, but the eye seems to be equally susceptible from the time when each individual structure begins to develop from one particular gestational stage until birth. However, it is established that craniofacial abnormalities are definitely related to prenatal alcohol exposure in a dose response manner in man, and the critical period for alcohol teratogenicity has been confirmed as being early in the first trimester.[11] It is further supported by the eye malformations in mouse experiments.[12]

Thirdly, the dose response factor is important during different stages of embryogenesis. The dosage of the teratogens may determine the severity of damage during the development of different structures of the eye.

It is difficult to determine the exact amount of maternal alcohol ingestion during pregnancy. Binge drinking is particularly common in alcoholic women, and periodical high blood alcohol levels may occur throughout pregnancy. All of our cases have a strong history of maternal alcohol abuse, especially during the first trimester. Half of them are children of single parent with poor social background and frequently failed to attend clinic for follow-up. Apart from ocular anomalies the systemic side effects of alcohol are detrimental to the physical and mental development of the child. These side effects include an increased risk of frequent infections, failure to thrive, multiple operations for various structural deformities, mental retardation, and visual deficit. Therefore preventive measures and education are imperative for women with chronic alcohol addiction. It is important to highlight the damage caused by alcohol in the period before pregnancy is recognised.

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# Regressed retinopathy of prematurity and its sequelae in children aged 5–10 years

Juan E Gallo, Gerd Holmström, Ulla Kugelberg, Bo Hedquist, Gunnar Lennerstrand

## Abstract

**Regressed retinopathy of prematurity (ROP) and its sequelae were studied in children born prematurely (<1501 g birth weight and/or <33 weeks gestational age) in Stockholm county during 1976–81. Through various searches of the records at the different eye departments and other sources in Stockholm county we found that 134 out of a total of 528 premature babies (25·4%) had needed ophthalmic care for different reasons. They were re-examined and reliable information on the fundus could be obtained for 105 of them. The frequency of regressed ROP was 45·5%. Severe forms with vitreoretinal scarring and retinal traction were seen in 9·7% of cases and moderate forms with pigmentary changes and/or vitreoretinal interphase changes in 35·8%. The sequelae of regressed ROP were mainly reduction of visual acuity and myopia. Children with a birth weight below 1000 g and a gestational age <30 weeks presented the highest rate of regressed ROP (68·5% and 61·9%) and ocular abnormalities.**

Retinopathy of prematurity (ROP) is known as a potentially blinding disease. Phelps has estimated that 8% of infants with a birth weight of 1000 g or less become blind from ROP in the United States.[1] In addition a broad spectrum of ocular abnormalities have been reported as complications of ROP.[2–5]

In the last decade important work has been done to prevent and diminish the severity of ROP.[6–8] We have conducted a retrospective study in prematurely born children in Stockholm county during 1976–81 in order to investigate the occurrence of ocular abnormalities. This paper deals with regressed ROP and its sequelae. A comparative study on the prevalence of visual impairments, refractive errors, and ocular motility disorders in premature babies and a control group of full-term babies will be reported separately. Some of the results have been published in a preliminary form.[9]

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## Material and methods

### EPIDEMIOLOGICAL CONSIDERATIONS

To be able to evaluate retrospective epidemiological studies of this kind some information on the Swedish health care system is needed. All births in Sweden are reported to the Board of Health and Welfare. Among other things the birth weight and the gestational age of the child is recorded together with information on the date of birth, the sex, etc. The accuracy of the registration has been tested (report 1977–02–10 of the Board of Health and Welfare). Errors in date of birth were found in 0·3%, in sex in 0·3%, and in weight in 1·0% of the reports. These numbers refer to the same period of time as our study.

The use of the 10-digit person identification number in different Swedish registers makes it fairly easy to obtain information on the patients within the health care system, and also to keep track of visits that the patients make to different hospitals and private offices.

During the period of our investigation, all prematurely born children in Stockholm county were cared for at five different neonatal units. The treatment schemes of the departments have been very similar, at least for the same period of time, and also quite advanced from an international standpoint.

Paediatric ophthalmology services are mainly provided at three departments in Stockholm county. All children below the age of 5 are referred to these centres with very few exceptions. The somewhat older children were sometimes referred to a limited number of ophthalmologists outside these centres. With this knowledge of the system for paediatric ophthalmic care it was fairly easy to obtain complete coverage of information on the groups of children that we were interested in.

During the period 1976–81 prematurely born children were not examined regularly by ophthalmologists in the neonatal wards, and there were no particular arrangements for ophthalmological follow-up of these children. However, they were included in the general health care system for children, which implies that the child was examined regularly at the health care centres for children and referred for ophthalmic investigation when needed. All children were screened for reduced visual acuity in each eye at the age of 3·5–4 years, and those who fell below the accepted limits were referred for ophthalmic examination. The rate of participation in these screening procedures is very high, about 95–98% of the population.[10] At visual acuity testing during first grade in school very few new cases of visual impairment are discovered when the screening at 3·5–4 years is done correctly.[11 12] Most of the early ocular problems of children should therefore have been discovered and cared for by the age of 5 years.

### POPULATION OF PREMATURE INFANTS

From the birth registers of the Swedish National Board of Health and Welfare all preterm children born in Stockholm county from 1 January 1976 to 31 December 1981 (a six-year period) were selected for the study if they had a birth weight <1501 g and/or a gestational age <33 weeks. Gestational age was determined according to the method of Dubowitz *et al.*[13] Our criteria for prematurity in this study included birth weight and/or gestational age, since we wanted to reduce the number of children that had been reported with an incorrect value in any of the parameters. In recent studies the most common criterion has been birth weight below 1500 g alone. However, the mean birth weight of Swedish prematures at 32 weeks gestation is 1750 g. The limit 1500 g would have eliminated many quite premature children in our material. Nonetheless, prematures with a birth weight ≥2000 g were excluded from the study.

The population of prematures consisted of 528 children, not counting those who had died or moved from the area. The distribution with regard to birth weight and other details of the premature population is shown in Table 1.

By means of listings of the 10-digit person identification numbers of the premature children manual searches were made at the archives of ophthalmology departments and other sources in Stockholm county as well as over the Stockholm county computer system. A total of 134 prematures had been seen by ophthalmologists and orthoptists for various reasons (Table 1). The charts of these children were obtained from the departments, and they were analysed with regard to the ophthalmological parameters listed below. The study was approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden.

### OPHTHALMIC EXAMINATION

Every child underwent a standard examination of visual function and ocular motility. If the patient had been examined repeatedly, data from the last report was used in this study.

*Visual acuity and refractive errors.* Visual acuity was determined with Snellen charts adjusted to the age of the child. Blindness was defined as a visual acuity of less than 0·03 (2/36) in the better eye. Refraction was done with cycloplegia. A measure of static refraction was taken as that with which the patient achieved the best visual acuity. Spherical equivalents have been calculated in cases with astigmatic refractive errors.

*Binocular abnormalities.* The ocular motility examination included determination of versions, near point of convergence, and cover/uncover tests at near and distance fixation. When needed the patients were also examined with the Maddox cross at 5 m and the Maddox wing test for near fixation.

Ocular deviations were determined with a prism cover test when the patient was wearing appropriate correction of refractive errors. Strabismus was defined as manifest or intermittent heterotropia. A manifest or intermittent deviation of less than 10 prism dioptres was classified as microtropia.

*Table 1 Premature population. Distribution according to birth weight (grams)*

| | *<1000* | *1000–1500* | *1501–1999** | *Total* |
|---|---|---|---|---|
| Number of births | 148 | 443 | 274 | 865 |
| Survivors | 48 | 311 | 242 | 601 |
| Rate of survival | 32·4% | 70·2% | 88·3% | 69·5% |
| Number moved away | 5 | 37 | 31 | 73 |
| Number available | 43 | 274 | 211 | 528 |
| Number of ophthalmic patients | 19 | 79 | 36 | 134 |
| Rate of ophthalmic care | 44·1% | 28·8% | 17·0% | 25·4% |

*Only patients <33 weeks of gestational age.

*Ophthalmoscopic examination.* Information on ROP was obtained in the following manner. The records of the 134 preterm children were carefully screened. Five patients had undergone an examination under anaesthesia by experienced ophthalmologists, and the information contained in the records was considered to be sufficient for our study. Most other patients had not been examined by indirect binocular ophthalmoscopy, and peripheral changes might have been missed. We decided to perform a fresh eye fundus examination in these patients. In spite of large efforts 27 patients did not come for the examination, while 102 complied. Mydriatic drops were used to obtain a clear view of the retinal periphery. The fundus was examined with the indirect binocular ophthalmoscope and a 20 dioptre lens. The scleral depressor could not be used in any of these children aged 5–10 years. In two of the 102 patients the retinal periphery was impossible to examine clearly owing to manifest nystagmus in one patient and severe miosis in the other, who was treated with pilocarpine for congenital glaucoma. Thus exact information on fundus conditions was available for 105 of the 134 patients (see also Table 2).

In our classification of regressed ROP we have followed the suggestions of the International Committee for the Classification of late stages of ROP.[14] The committee has pointed out that regressed ROP has a broad spectrum of eye fundus abnormalities, so wide that it does not allow investigators to classify them in different stages. However, to bring about some order in the various ophthalmoscopic findings the committee has suggested recording them topographically into peripheral and posterior changes, and then a subdivision can be made into vascular and vitreoretinal changes. In our study we have also included a subdivision into severe and moderate regressed ROP in order to differentiate the degree of severity. The severe form included cases with vitreoretinal scarring equal to or larger than one optic disc diameter and the presence of tangential (transgel) traction of the retina. The remaining cases (with only pigmentary changes and/or vitreoretinal interphase changes) constituted the group of patients with moderate regressed ROP.

## Results

Table 1 shows the composition of the population of premature infants with respect to birth weight and other characteristics. Referrals for ophthalmic examination were commonest in the children with the lowest birth weights (<1000 g). The mean number of examinations in the group of patients was 8·7 times (SD 7·9, range 1–62), including those examinations made before the age of 5 years in children with severe ROP. One hundred and thirteen children (84·3%) had been seen three or more times by ophthalmologists or orthoptists.

Myopia was found in 33 children (24·6% of the children under ophthalmic care), unilateral in 14 and bilateral in 19 cases. Results of testing for

*Table 2 Regressed ROP and its relation with ocular abnormalities, immaturity, and birth weight*

| | *SSROP (n=13)* | *MRROP (n=48)* | *S+MRROP (n=61)* | *WRROP (n=44)* | *IF-Inform (n=29)* | *Total (n=134)* |
|---|---|---|---|---|---|---|
| Ocular motor disorders | | | | | | |
| Strabismus | 7 (53·8%) | 17 (35·4%) | 24 (39·3%) | 19 (43·2%) | 9 (31·0%) | 52 (38·8%) |
| Nystagmus | 5 (38·4%) | 3 (6·2%) | 8 (13·1%) | 1 (2·3%) | 4 (13·8%) | 13 (9·7%) |
| Refractive errors | | | | | | |
| Myopia | 8 (61·5%) | 14 (29·1%) | 22 (36·1%) | 5 (11·4%) | 6 (20·7%) | 33 (24·6%) |
| Myopia >3 D | 7 (53·8%) | 2 (4·2%) | 9 (14·7%) | 1 (2·3%) | 2 (6·9%) | 12 (8·9%) |
| Anisometropia ≥1 D | 8 (61·5%) | 10 (20·8%) | 18 (29·5%) | 8 (18·2%) | 5 (17·2%) | 31 (23·1%) |
| Visual acuity | | | | | | |
| ≤0·6 (6/9) WE | 9 (69·2%) | 6 (12·5%) | 15 (24·6%) | 6 (13·6%) | 10 (34·5%) | 38 (28·3%) |
| ≤0·6 (6/9) BE | 6 (46·1%) | 3 (6·2%) | 9 (14·7%) | 3 (6·8%) | 7 (24·1%) | 19 (14·2%) |
| ≤0·3 (6/18) WE | 6 (46·1%) | 1 (2·1%) | 7 (11·5%) | – | 3 (10·3%) | 10 (7·5%) |
| ≤0·3 (6/18) BE | 3 (23·1%) | – | 3 (4·9%) | – | 1 (3·4%) | 4 (3·0%) |
| Blind | 2 (15·4%) | – | 2 (3·3%) | – | – | 2 (1·5%) |
| Birth weight | | | | | | |
| <1000 g | 5 (38·5%) | 8 (16·7%) | 13 (21·3%) | 4 (9·1%) | 2 (6·9%) | 19 (14·2%) |
| 1000–1500 g | 7 (53·8%) | 29 (60·4%) | 36 (59·0%) | 24 (54·5%) | 19 (65·5%) | 79 (58·9%) |
| 1501–1999 g | 1 (7·7%) | 11 (22·9%) | 12 (19·7%) | 16 (36·4%) | 8 (27·6%) | 36 (26·9%) |
| Gestational age | | | | | | |
| 26–29 weeks | 9 (69·2%) | 17 (35·4%) | 26 (42·6%) | 11 (25·0%) | 5 (17·2%) | 42 (31·3%) |
| 30–32 weeks | 4 (30·8%) | 21 (43·7%) | 25 (41·0%) | 28 (63·6%) | 19 (65·6%) | 72 (53·8%) |
| 33–37 weeks | – | 10 (20·9%) | 10 (16·4%) | 5 (11·4%) | 5 (17·2%) | 20 (14·9%) |

Abbreviations: severe regressed ROP (SRROP); moderate regressed ROP (MRROP), without regressed ROP (WRROP), better eye (BE); worse eye (WE); incomplete fundus information (IF-Inform)

anisometropia and visual acuity are shown in Table 2.

Strabismus was found in 52 prematures (38·8%), and of them esotropia was seen in 24, exotropia in 13, and microtropia in 15. A group of 13 prematures (9·7%) had nystagmus of different types: six horizontal, two end-point, and five latent nystagmus, respectively.

### REGRESSED ROP

A total of 61 patients (45·5%) presented signs of regressed ROP. Severe forms of regressed ROP was seen in 13 patients (9·7%) and moderate forms in 48 patients (35·8%).

Regressed ROP occurred most commonly in children with a low birth weight and a low gestational age. It was seen in 13 out of 19 patients with a birth weight below 1000 g (68·5%) and in 36 out of 79 patients between 1000–1500 g (45·6%). Regarding gestational age, 26 out of 42 children <30 weeks (61·9%) and 25 out of 72 children between 30–32 weeks (34·7%) had signs of ROP.

Vitreoretinal scarring was larger than 3 optic disc diameters in all patients but one. Dragging of retina over the disc was found in five patients. A tractional retinal detachment was seen in three patients, while distortion of macula was diagnosed in four patients. Further information on posterior vitreoretinal changes is given in Table 3.

Table 4 highlights the peripheral vitreoretinal findings. Pigmentary changes were seen in 50 children, vitreous membranes in four, and lattice-like degeneration in one child.

### REGRESSED ROP AND ITS RELATION WITH OCULAR ABNORMALITIES

Two patients (1·5%) were blind from ROP. Three patients with regressed ROP (2·2%) presented a visual acuity ≤0·3 (6/18) in the better eye, while seven patients (5·2%) had a visual acuity ≤0·3 (6/18) in the worse eye (Table 2). The majority of these patients had the severe type of ROP, and only one of them showed the moderate form.

The relation between regressed ROP and refractive errors can be seen in Table 2. Among 33 myopic patients and 31 anisometropic patients signs of regressed ROP were seen in 22 (66·7%) and 18 patients (58·1%), respectively.

Fifty-two patients with strabismus and 13 with nystagmus constituted the group of children with ocular motility disorders. Regressed ROP was found in 24 patients with strabismus (46·1%) and in eight patients with nystagmus (61·5%).

### SEVERITY OF REGRESSED ROP

The severe form of regressed ROP was diagnosed in 26·3% of prematures with a birth weight less than 1000 g, in 8·9% of those between 1000–1500 g, and in 2·8% of prematurely born children

*Table 3 Ophthalmoscopic findings: posterior ROP changes*

| | *Right eye* | *Left eye* | *No of eyes* | *No of patients* | *Rate (n=134)* |
|---|---|---|---|---|---|
| Vitreous haemorrhage | 1 | – | 1 | 1 | 0·74% |
| Straightening of vessels | – | 2 | 2 | 2 | 1·5% |
| Pigmentary changes | 1 | 1 | 2 | 1 | 0·74% |
| Distortion/ectopia of macula | 3 | 4 | 7 | 4 | 3% |
| Vitreous membranes | 1 | – | 1 | 1 | 0·74% |
| Dragging of retina over disc | 3 | 4 | 7 | 5 | 3·7% |
| Tractional retinal detachment | 3 | 3 | 6 | 3 | 2·2% |

*Table 4 Ophthalmoscopic findings: peripheral ROP changes*

| | *Right eye* | *Left eye* | *No of eyes* | *No of patients* | *Rate (n=134)* |
|---|---|---|---|---|---|
| Pigmentary changes | 34 | 40 | 74 | 50 | 37·3% |
| Vitreoretinal interface changes | 1 | 4 | 5 | 4 | 3·0% |
| Vitreous membranes | 2 | 3 | 5 | 4 | 3·0% |
| Lattice-like degeneration | 1 | – | 1 | 1 | 0·74% |
| Tractional retinal detachment (only in periphery) | – | 1 | 1 | 1 | 0·74% |

in the 1501–1999 g bracket (see Table 2). The same degree of severity was found in 21·4% of children with a gestational age <30 weeks, in 5·5% of those between 30–32 weeks, and in none of the patients with a gestational age >32 weeks.

Among 13 patients affected with severe regressed ROP eight had anisometropia ≥1 D, eight had myopia, and of these patients seven had myopia of more than 3 D. These were higher values than in patients with moderate regressed ROP or in those without regressed ROP (Table 2).

### OCULAR ABNORMALITIES IN PATIENTS WITH INCOMPLETE FUNDUS EXAMINATION

Only one of the 29 patients with incomplete fundus examination had poor vision – that is, visual acuity below or equal to 0·3 (6/18) in the better eye – but three of them had a visual acuity ≤0·3 (6/18) in the worse eye, and 10 patients had a visual acuity level ≤0·6 (6/9) in the better eye. Six of the children not examined were myopic, while five had anisometropia ≥1 D. With regard to ocular motility disorders, strabismus and nystagmus were present in nine and four patients, respectively (Table 2).

## Discussion

This report on the occurrence and characteristics of regressed ROP in prematurely born children is part of a retrospective study of the ocular changes in 528 prematures born in Stockholm county during the years 1976–81.

Although our study suffers from the lack of information on acute ROP, we believe this is not an impediment to analysing the fundus findings of premature children aged 5–10 years. However, it may be reasonable to suggest that some of the so-called signs of regressed ROP in our study could have been the result of conditions other than prematurity. None the less, this is hardly the case in our population of patients. First of all, none of the children with signs of regressed ROP had a history of a disease which can simulate ROP changes in its regressed form, such as familial exudative retinopathy, persistent hyperplastic vitreous, incontinentia pigmenti, X-linked retinoschisis, retinal dysplasia, toxoplasmosis, and cytomegalic inclusion disease.[15] Moreover, most of the children in our study had a long follow-up, and no information on other ocular pathology and systemic diseases with possible fundus changes was found in the records than what is reported here. We believe that the risk of having misdiagnosed some of the fundus findings is very low.

Most of the findings on regressed ROP were obtained at a re-examination of the children during 1987–8, when they were 6–11 years old. Based on these findings the incidence was 45·5%. However, among the 134 children who had been referred to ophthalmologists for different reasons and who constitute our study group, 27 (20%) did not come for the re-examination. Available data showed that the drop-outs represented 25% of the children with VA ≤0·3 (6/18), 37% of those with VA ≤0·6 (6/9) in the better eye, 18% of the myopic children, 16% of the patients with anisometropia, 30% of the patients with nystagmus, and 17% of those with strabismus. Since there is a connection between such findings and ROP, it is very likely that the number of patients with regressed ROP would have been higher if it had been possible to examine all the patients properly. Therefore the true incidence of regressed ROP in premature children born in Stockholm and who needed ophthlamic care for different reasons can be expected to fall within the range 45·5%–65·6%.

It is well established that ROP is commoner in premature babies of low birth weight than others. In our material regressed ROP was seen in about two-thirds of the prematures with birth weights <1000 g. Similar findings were seen with regard to immaturity. More than half the children with gestational age <30 weeks had ROP.

The most severe forms of regressed ROP were seen in two blind children. Severe regressed ROP was connected with reduced visual acuity ≤0·3 (6/18) in the better eye – that is, with visual handicap. Children with moderate regressed ROP or with no signs of regressed ROP never showed reduced vision to this level.

The role of ROP in the development of ocular abnormalities is well established.[2-5 16] In our study a close association could be observed between regressed ROP and myopia, particularly between the severe forms of regressed ROP and high myopia, which is in accordance with previous reports.[4 17 18] The frequency of anisometropia was higher in children with regressed ROP than in those who did not present signs of this disease. Strabismus was slightly commoner in cases with regressed ROP, and patients with nystagmus suffered more often than not from sequelae of ROP. Refractive errors are likely to represent developmental changes in the eye, probably induced by the same processes as those underlying regressed ROP. Strabismus and nystagmus, on the other hand, probably reflect developmental changes in the central nervous mechanisms of binocular vision and oculomotor control, and would therefore not be correlated with the severity of regressed ROP.

With regard to the ophthalmoscopic findings, pigmentary changes were the commonest signs of regressed ROP. Although the evaluation might be subjective, it is interesting to note that a broad spectrum of pigmentary changes can be found. According to the observations of Foos,[19] focal pigmentations correspond microscopically to scattered pigmentation of the retina, as a consequence of the intraretinal proliferation at the time of injury. Pigmentary lines might also be the result of intraretinal proliferations or the ophthalmoscopic appearance of retroretinal membranes. These membranes have been reported in advanced cases of ROP.[20] In our patients we could not see any retroretinal membrane in cases without retinal detachment.

Vitreous membranes were observed in six eyes of four patients with regressed ROP in our study. These membranes may be glial in origin, but, as Foos has pointed out,[20] they can be seen in cases of arrested ROP in which the extraretinal vascular component has been involuted. The clinical significance of these membranes in arrested ROP is not well understood. It should be noted that all these patients except one had visual acuity of 0·5 (6/12) or better in the worse eye, which means that central retinal function was not markedly affected. One patient had normal ocular motility, but the others had strabismus and/or nystagmus. Unfortunately we have no information on the retinal conditions of these children during the neonatal period and early infancy, and we cannot evaluate the possible morphological changes of these membranes during the time preceding our examination.

The high frequency of regressed ROP in our material strongly indicates that prematurely born children are an ophthalmological risk group, with increased incidence of refractive errors, strabismus, and retinal complications. They must therefore be carefully followed up during the period of visual development in order to prevent visual dysfunction by intervention as early as possible.

Finally, paediatricians and ophthalmologists must continue jointly to investigate the conditions that predispose to ROP in the hope of preventing or at least diminishing the severity of the disease. For this purpose a study of risk factors in ROP has been performed.

Part of the results of this paper were presented at the 18th European Strabismological Association meeting in Krakow, Poland, on 21–22 October 1989.

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# Evaluation of bilirubin as possible protective factor in the prevention of retinopathy of prematurity

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## Abstract

**Retinopathy of prematurity (ROP) appears to be a multifactorial disease, the prevention of which is probably impossible even with the most accurate methods of blood-gas monitoring and oxygen restrictions. The oxidative processes and consequent formation of free radicals are probably influenced by the availability of various antioxidants in the immature retina. Bilirubin, the end product of haem catabolism, has recently been regarded as a potential physiological antioxidant. In order to test the suggestion as to the possible effect of bilirubin in reducing the incidence of ROP a retrospective study was undertaken of the medical records of 151 neonates born between 1984 to 1988 who weighed less than 1500 g. Of these, 78 had various degrees of ROP, whereas 73 had no ROP and served as a control group. The daily mean bilirubin values were analysed in accordance with gestational age and birth weight as well as the severity of ROP, and the results were compared with those obtained for the control group. The results showed no correlation between bilirubin levels and severity of ROP in all subgroups of gestational age and birth weight. These findings indicate that there is no apparent protective effect of bilirubin on the development of ROP.**

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During the past few decades there have been dramatic advances in the care of critically ill newborn babies, resulting in the greatly improved survival of infants with extremely low birth weights. Phelps[1] estimated that 30–35% of infants with a birth weight of 1000 g or less will develop cicatricial retinopathy of prematurity, with 8% becoming blind. As ROP appears to be a multifactorial disease,[2-8] its complete prevention, even by the most accurate methods of monitoring blood gases and oxygen restriction, has been assumed to be impossible. However, the search for possible influencing factors continues.

Current data indicate that oxidative processes in the tissues may be of vital importance in the initiation of the disease.[3,4] These oxidative processes and the consequent formation of free radicals are probably influenced by the availability of various antioxidants in the immature retina.[2-8] Stocker *et al*[9-11] have shown that bilirubin is a potential physiological antioxidant. The preliminary data collected by Heyman *et al*[12] suggested that bilirubin may play a protective role in the prevention of ROP. We report here the findings of a retrospective study carried out to evaluate the possible correlation between bilirubin levels and severity of ROP as related to gestational age and birth weight in a group of neonates weighing less than 1500 g.

*Table 1 Infant groups according to ROP stage and gestation age*

| *Gestational age (wks)* | *Stage of ROP* *0* | *1* | *2* | *3* | *Total* |
|---|---|---|---|---|---|
| ≤27 | 7 | 5 | 12 | 16 | 40 |
| ≤28 | 8 | 6 | 18 | 23 | 55 |
| ≤29 | 17 | 11 | 23 | 25 | 76 |
| ≤30 | 28 | 14 | 26 | 28 | 96 |
| ≤31 | 43 | 17 | 27 | 28 | 115 |
| ≤32 | 52 | 19 | 28 | 29 | 128 |
| ≤33 | 64 | 19 | 28 | 29 | 140 |
| ≤34 | 73 | 20 | 29 | 29 | 151 |

## Patients and methods

We reviewed the medical records of all neonates with a gestational age of 34 weeks or less and weighing less than 1500 g who were admitted to the neonatal intensive care unit from January 1984 to December 1988: 151 premature infants met these criteria. ROP was found in 78, whereas 73 had no ROP and served as controls.

The 78 infants with ROP were grouped according to the severity of ROP on the basis of the International Classification of ROP.[13] Twenty had stage 1 disease, 29 had stage 2, and 29 had stage 3 ROP. None of the babies had stages 4 or 5. To test the possible correlation between bilirubin levels and ROP in neonates with different gestational age and birth weight we divided the patients into several subgroups. Table 1 gives the eight gestational age subgroups and Table 2 the four birth weight subgroups.

The mean daily bilirubin levels in the first 14 days of life were calculated. These values were plotted in the different ROP, gestational, age and birth weight subgroups. The data were analysed statistically by Student's *t* test.

## Results

The mean bilirubin level of the first 14 days was 5·95 mg/dl (102 μmol/l) in babies with ROP as compared with 6·05 mg/dl (103 μmol/l) in neonates without retinopathy; this difference has no statistical significance ($p>0{\cdot}05$).

The daily mean bilirubin values were very similar in infants with ROP as compared with those without ROP ($p>0{\cdot}05$) (Fig 1). Further-

*Table 2 Infant groups according to ROP stage and birth weight*

| *Birth weight (g)* | *Stage of ROP* *0* | *1* | *2* | *3* | *Total* |
|---|---|---|---|---|---|
| <750 | – | 1 | – | 2 | 3 |
| <1000 | 4 | 6 | 15 | 18 | 43 |
| <1250 | 33 | 11 | 25 | 27 | 96 |
| <1500 | 73 | 20 | 29 | 29 | 151 |

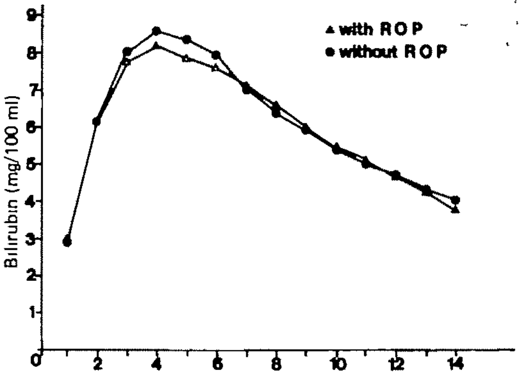

*Figure 1 Presence or absence of ROP in relation to bilirubin levels. SI conversion: mg/100 ml×17·1=μmol/l.*

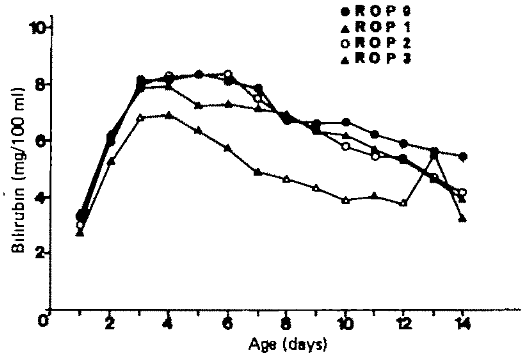

*Figure 3 Bilirubin levels in accordance with ROP stage in prematures born ≤27 weeks of gestation. SI conversion: mg/100 ml×17·1=μmol/l.*

more, comparison of the bilirubin levels in the various ROP stage groups revealed no statistically significant difference between patients with no ROP and patients with ROP stages 1, 2, and 3 (p>0·05) (Fig 2). In the gestational age subgroups of less than 27 to 34 weeks mean bilirubin levels ranged between 5·99 and 6·27 g/dl (102 and 107 μmol/l) in the various ROP stages. In the birth weight subgroups of less than 750 to 1500 g the mean bilirubin levels ranged between 4·83 and 5·99 mg/dl (83 and 102 μmol/l). These data shows no statistically significant difference between the various gestational age and birth weight subgroups (p>0·05).

Fig 3 serves as an example of this trend in gestational age subgroup of 27 weeks and less, and Fig 4 is an example of the mean daily bilirubin levels in the birth weight subgroup of less than 1250 g.

These results show that the bilirubin level pattern was very similar in all groups of gestational age and birth weight.

## Discussion

It has recently been suggested that endothelial cell damage in the retina is caused by oxygen-derived free radicals, which are probably more harmful in premature infants owing to lower levels of antioxidants in the immature retina.[3 4]

In a post-mortem study of the vitreous humour of premature babies with respiratory distress syndrome Saugstad and Tognum[14] found high levels of hypoxanthine. This was believed to be not only a sign of hypoxia but also a potential generator of oxygen radicals. Bilirubin, the end product of haem catabolism in mammals, is generally regarded as a potentially cytotoxic lipid-soluble waste product that needs to be excreted. However, the data presented by Stocker *et al*[9–11] support the concept of a beneficial role of bilirubin as a physiological, chain-breaking antioxidant.

Heyman *et al*[12] subsequently raised the question whether bilirubin might have a protective effect in the prevention of ROP. They found that in neonates with ROP (stages 2, 3, or 4) bilirubin levels from day 4 were considerably lower than those in neonates with stage 1 ROP or no ROP, and suggested that bilirubin may have a protective effect in the prevention of ROP.

Our retrospective study of premature neonates, weighing less than 1500 g and with gestational age of 34 weeks or less, shows a very similar pattern of mean bilirubin levels during the first 14 days of life among infants with stages 1, 2, and 3 ROP as well as infants with no ROP. There were no statistically significant differences in bilirubin levels when considered in relation to severity of ROP, gestational age, or birth weight. These results therefore do not support the concept that bilirubin is a possible protective factor in the prevention of ROP. Furthermore, we assume that bilirubin levels in the first days of life in premature babies are probably not correlated with the development of ROP.

As the main pathological effect of ROP is ischaemia of peripheral retinal areas due to impaired blood supply, it is reasonable to assume that bilirubin levels in the affected regions are low. It is therefore possible that these low

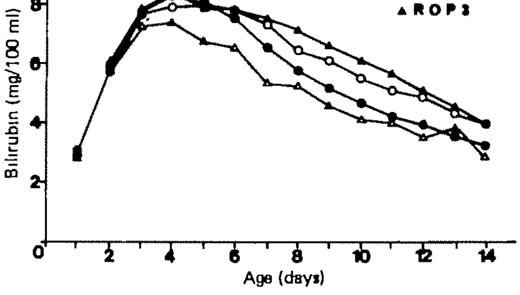

*Figure 2 Mean bilirubin levels in accordance with ROP stage. SI conversion: mg/100 ml×17·1=μmol/l.*

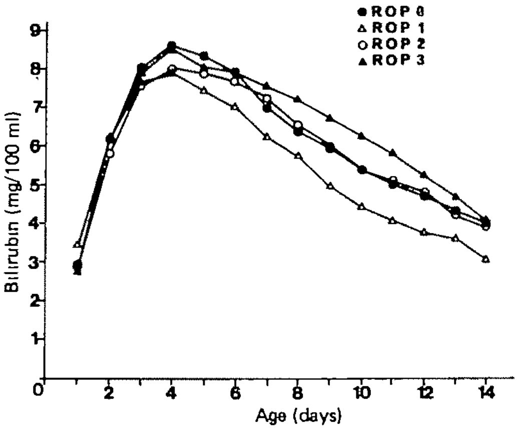

*Figure 4 Bilirubin levels in accordance with ROP stage in prematures with birth weight <1250 g. SI conversion: mg/100 ml×17·1=μmol/l.*

bilirubin levels may be insufficient for the antioxidative potential effect of bilirubin.

Another explanation of the undetected antioxidative effect of bilirubin may be due to the fact that this report reviewed bilirubin levels in the first 14 days of life, a period in which bilirubin is known to be physiologically high. As ROP tends to not appear before 6 weeks of age, it is possible that the time interval between the decrease to normal bilirubin levels and the appearance of ROP is long enough to diminish its protective effect in preventing the disease.

This study was presented in partial fulfilment of the requirements of Tel Aviv University Sackler Faculty of Medicine for the MD degree of Joseph Gold

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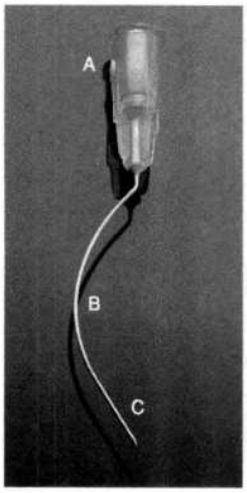

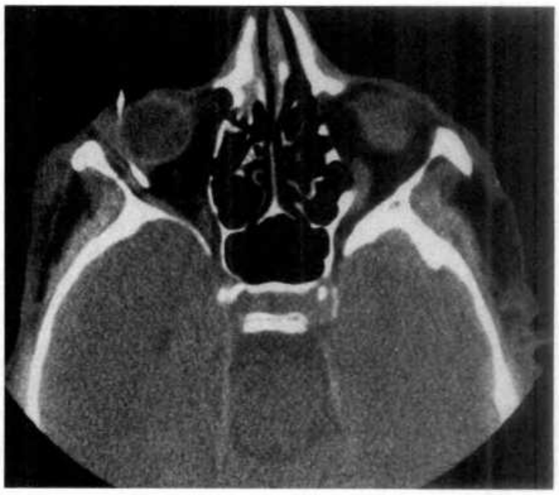

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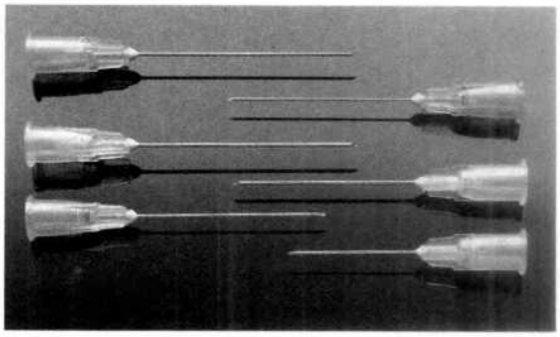

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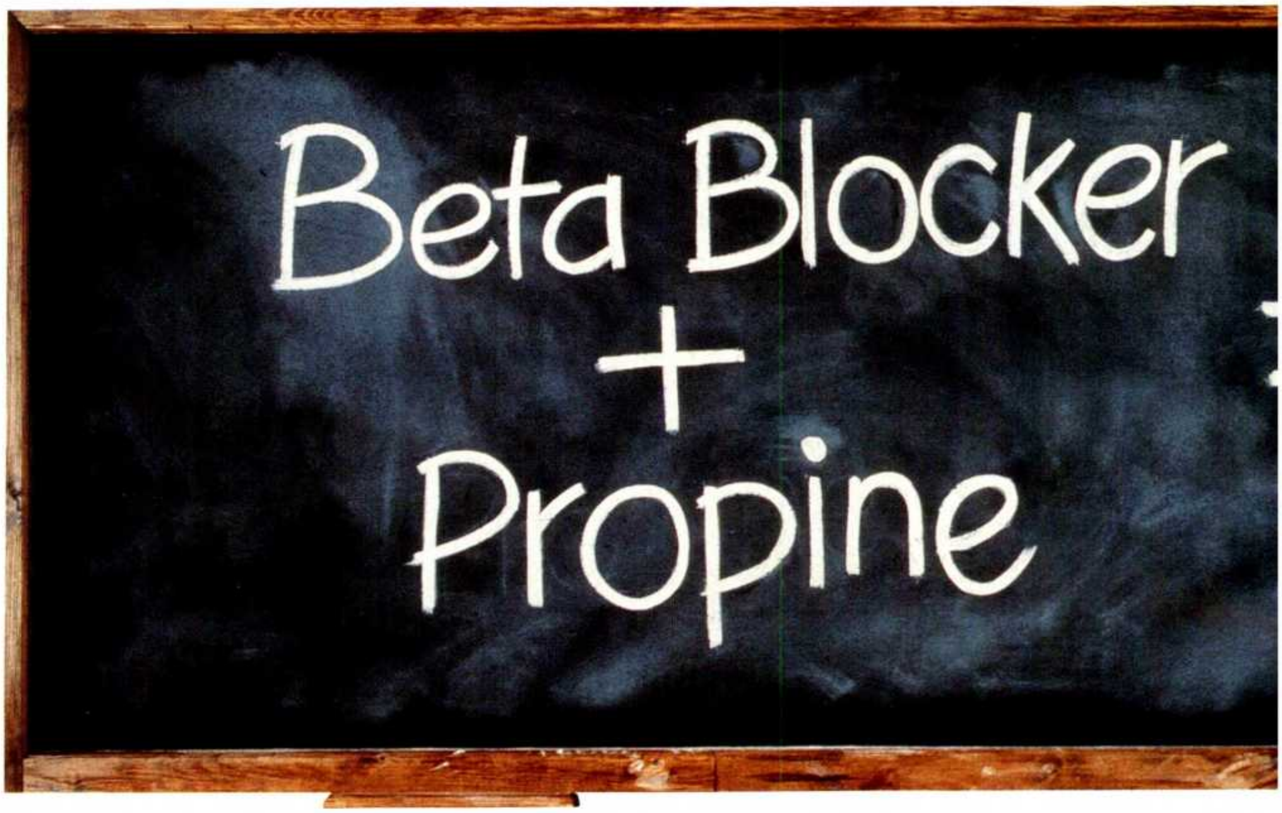

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*Precautions:* Dipivefrin should be used with caution in patients with narrow an
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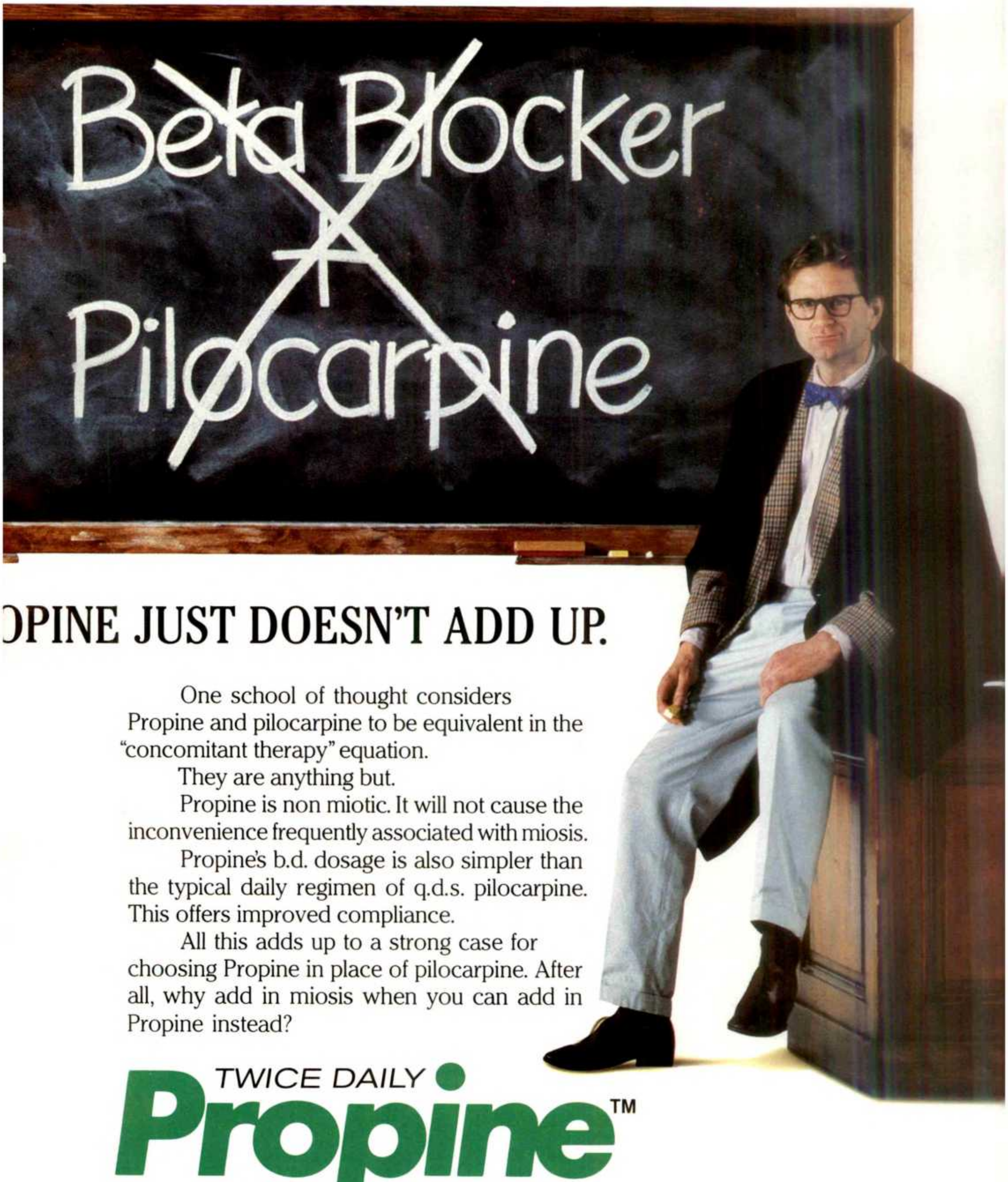

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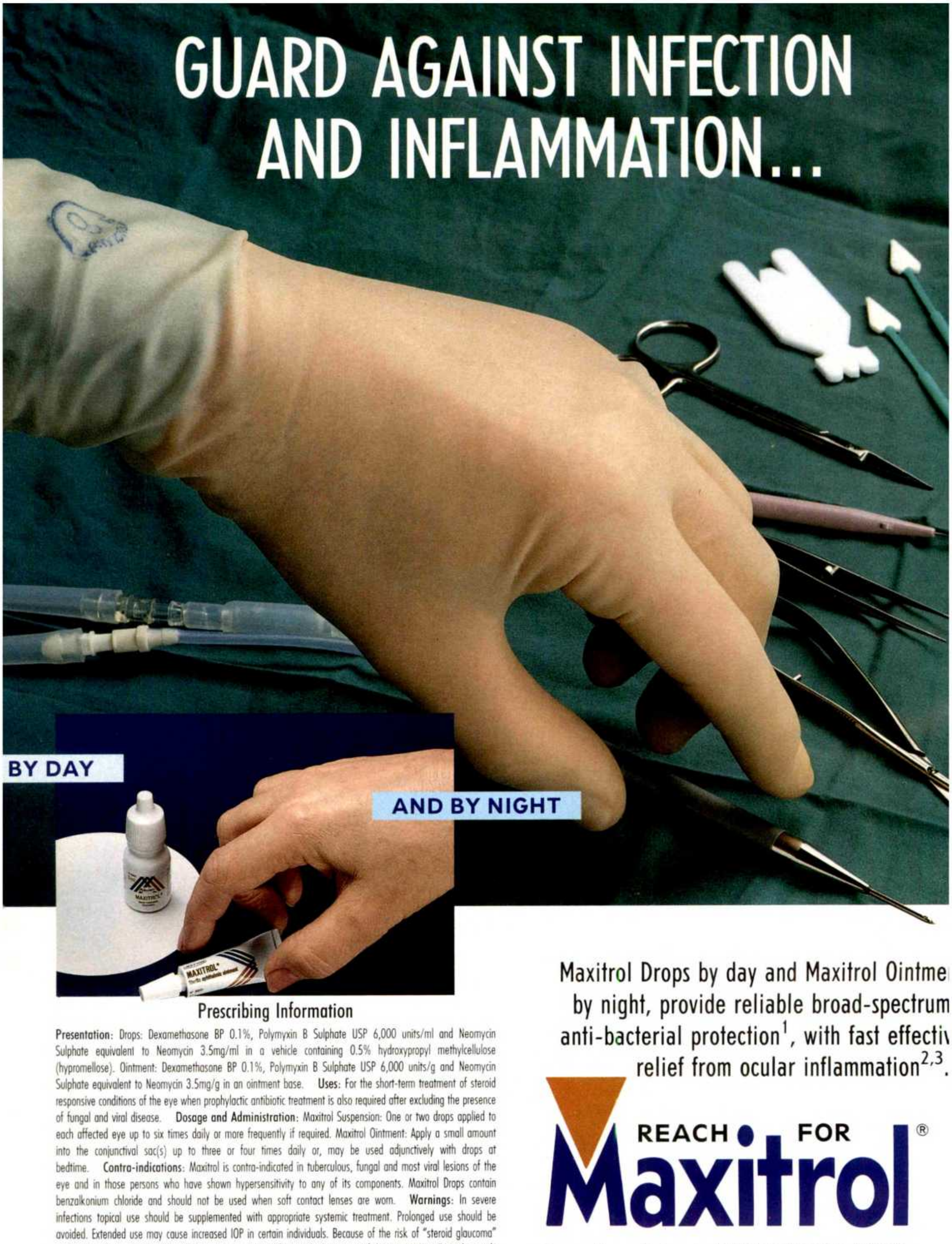

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*British Journal of Ophthalmology*, 1991, 75, 535–537

# Supplemental gas tamponade after conventional scleral buckling surgery – a simple alternative to surgical revision

David R Worsley, Rodney H B Grey

**Abstract**

**Supplemental intravitreal gas injection was used in the early postoperative period in an attempt to achieve long term retinal reattachment in 11 cases of failed scleral buckling surgery. Success was dependent on the presence of a correctly placed scleral buckle underlying all breaks. Surgical revision was thereby avoided in these patients. However, when the scleral buckle was inadequate the technique failed.**

The incidence of failure of retinal detachment surgery is 5–10%.[1] Failure of the primary surgical procedure may have several unfavourable consequences, most notably the development of proliferative vitreoretinopathy (PVR), which is the main reason for long term failure of reattachment.[2] Surgical revision increases the risk of complications, lengthens morbidity, and is itself implicated in the genesis of PVR.

A simple method of restoring retinal attachment following failure in the early postoperative period may avoid surgical revision, lessen the risk of PVR, and should therefore improve the success rate for long term retinal reattachment.

Intravitreal gas injection is a widely used method of retinal break tamponade. 'Pneumatic retinopexy' is considered an alternative to scleral buckling surgery and may be used in the management of established failure of scleral buckling surgery.[3] Bedside intravitreal air injection has been successfully used for persistent subretinal fluid (SRF) in seven patients after non-drainage scleral buckling procedures.[4]

We have reviewed our use of a technique of supplemental intravitreal gas injection for redetachment in the early postoperative period after scleral buckling surgery. Our aim was to reattach the retina by the simplest effective method as soon as progressive redetachment was observed.

## Patients and method

### PATIENT SELECTION CRITERIA

Seven patients had a primary rhegmatogenous retinal detachment managed by scleral buckling surgery. Four criteria were used for selection of patients considered suitable for supplemental gas injection: (1) an increase or reappearance of SRF was documented; (2) an open break was visible; (3) all open breaks lay between 8 and 4 o'clock (clockwise); and (4) the scleral indent was judged to be in the correct position and of adequate height relative to all open breaks. Patients with static SRF were specifically excluded, as there may be spontaneous retinal reattachment with time.

In all but one patient increasing SRF was observed within the first two to seven days of surgery and in the other patient within three weeks of surgery.

In addition a further four patients who did not fulfill criterion 4 were treated, as we made a clinical judgment that, despite the inadequacy of the buckle, the eye looked likely to benefit. One patient had an additional tear totally unsupported by a circumferential indent; two had horseshoe tears incompletely supported anteriorly; and one had a tear incompletely supported laterally by a narrow radial indent. In all these four cases the break was close to the retinal pigment epithelium.

### METHOD

Retrobulbar anaesthesia was necessary because we found topical anaesthesia to be insufficient in the early postoperative period. The patients lay on their side with the operated eye uppermost and facing the surgeon, who was seated wearing an indirect ophthalmoscope.

Using an aseptic technique the surgeon inserted a wire speculum and instilled chloramphenicol 1% eyedrops into the conjunctival sac. With calipers a point 3·5 mm posterior to the limbus was marked on the temporal conjunctiva. A 1 ml syringe with a 30 G needle and containing 0·5–0·8 ml of 100% sulphur hexafluoride (SF6) gas was inserted through this point into the centre of the vitreous cavity. The needle was visualised and then withdrawn until the tip was judged to be just within the vitreous cavity. The gas was injected to form a single bubble and the needle withdrawn. The patient was immediately rolled to the opposite side to prevent loss of gas via the injection site.

The central retinal artery was assessed to ensure that there was perfusion. An attempt was made to select a volume of gas that resulted in the endpoint of artery pulsation. For most patients this volume was about 0·6–0·8 ml. If there was no central retinal artery perfusion, gas was withdrawn until arterial pulsation was observed. The patient was positioned so as to achieve gas tamponade of the retinal break(s). Positioning was maintained for two to five days.

Once reapposed to the indent the break was assessed to see whether there was a sufficient surround of cryotherapy. If this was not the case or if the cryotherapy was more than seven days old, then supplemental laser was applied. The binocular indirect laser delivery system was

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Table 1 *Adequate scleral buckle – successful*

| *Patient* | *Age* | *Sex* | *Configuration of primary detachment* | *Primary surgery* | *Time to gas injection (days post surgery)* | *VA Pre-* | *VA Post-* | *Follow-up (months)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | | *Injection* | | |
| 1 | 63 | F | STQ, SNQ, macula off, round hole | Cryotherapy, SRF drainage, circumferential tyre | 5 | 6/24 | 6/9 | 12 |
| 2 | 75 | F | STQ, SNQ, macula off, round holes | Cryotherapy, SF6 20%, circumferential tyre | 3 | HM | 6/18 | 8 |
| 3 | 64 | F | STQ, macula on, U tear | Cryotherapy, radial sponge | 4 | 6/6 | 6/9 | 9 |
| 4 | 59 | M | STQ, macula off, U tears | Cryotherapy, SRF drainage, radial sponge | 3 | HM | 6/36 | 11 |
| 5 | 64 | M | STQ, ITQ, macula off, round holes | Cryotherapy, SRF drainage, circumferential tyre | 4 | HM | 6/36 | 9 |
| 6 | 78 | M | STQ, ITQ, macula off, U tears | Cryotherapy, circumferential tyre | 17 | HM | 6/36 | 4 |
| 7 | 76 | F | STQ, SNQ, macula on, U tears | Cryotherapy, SRF drainage, radial sponge | 3 | 6/9 | 6/9 | 3 |

SNQ=superior nasal quadrant; INQ=inferior nasal quadrant; STQ=superior temporal quadrant; ITQ=inferior temporal quadrant; SRF=subretinal fluid; SF6=sulphur hexafluoride; HM=hand movements.

particularly useful, as the direct view was often difficult owing to the presence of a gas bubble and to the peripheral position of the breaks.

## Case reports

Two cases are described in more detail to illustrate the type of patient considered suitable for supplemental intravitreal gas injection.

### CASE 1

*Highly elevated break.* A 63-year-old woman with a right phakic eye developed an upper half bullous detachment with macular involvement due to a peripheral horseshoe tear at 11 o'clock. The visual acuity was 6/24. Primary surgery involved cryopexy, circumferential buckle, and subtotal drainage of SRF. The break remained highly elevated over the indent, and by the fourth postoperative day there was evidence of increasing subretinal fluid.

A supplemental intravitreal injection of 0·5 ml of 100% SF6 was given and the patient positioned. One day later the SRF was markedly reduced and the break flat on the indent. All SRF had been absorbed after five days. The retina remained flat with a visual acuity of 6/9 after 11 months' follow-up.

### CASE 2

*Communicating retinal fold.* A 75-year-old woman with a phakic right eye developed an upper-half detachment involving the macula due to several small round holes in the upper retinal periphery. The visual acuity was hand movements. Primary surgery involved cryotherapy, circumferential buckle, SRF drainage, and 20% SF6 intravitreal injection to reconstitute volume. The retina was initially flat, but after three days a small amount of SRF reformed and communicated with one of the retinal breaks via a meridional fold. Insufficient intravitreal gas remained for tamponade of the break. 0·7 ml of 100% SF6 was injected into the vitreous cavity and the patient positioned. The SRF was completely resorbed within six hours. Argon laser photocoagulation was applied to surround the break and to the retinal fold over the indent. After eight months' follow-up the retina was flat and the visual acuity was 6/18.

## Results

All seven patients who fulfilled the selection criteria had successful anatomical retinal reattachment (Table 1). The follow-up period ranged from three to 12 months and averaged eight months. In all cases complete resorption of SRF was observed. Recently accumulated SRF was resorbed rapidly (in several cases within a few hours), while longer standing SRF was resorbed over one to five days.

In contrast, of the four patients who did not fulfill selection criterion 4, none had retinal reattachment (Table 2).

The adequacy of the scleral buckle was a statistically significant factor in successful retinal reattachment in our cases (Fisher exact probability test, $p<0{\cdot}01$) (Table 3).

### COMPLICATIONS

It was our clinical impression two of the four patients with an inadequate scleral indent had a less favourable long term outcome as a direct result of the gas injection. These two patients

Table 2 *Inadequate scleral buckle – unsuccessful*

| *Patient* | *Age* | *Sex* | *Configuration of primary detachment* | *Primary surgery* | *Time to gas injection (days post surgery)* | *VA Pre-injection* | *Surgical revision* | *Final outcome* | *Final VA* | *Follow-up (months)* |
|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 77 | M | SNQ, INQ, macula on, U tears | Cryotherapy, circumferential sponge | 5 | CF | Vitrectomy, silicone oil | Phthisis | NPL | 9 |
| 9 | 59 | M | STQ, SNQ, macula on, U tears | Cryotherapy, SRF drainage, circumferential band | 21 | 6/9 | Encircling tyre, SRF drainage | Flat retina | 6/9 | 8 |
| 10 | 54 | F | STQ, SNQ, macula on, U tears | Cryotherapy, SRF drainage, radial sponge | 6 | 6/9 | Vitrectomy, silicone oil | Flat retina | HM | 6 |
| 11 | 44 | M | STQ, macula on, U tears | Cryotherapy, radial sponge | 4 | 6/9 | Adjustment of radial sponge | Flat retina | 6/9 | 4 |

SQN=superior nasal quadrant, INQ=inferior nasal quadrant; STQ=superior temporal quadrant; SRF=subretinal fluid; CF=count fingers; HM=hand movements; NPL=no perception of light

*Table 3 Summary of results*

| *Scleral indent* | *Number of patients* | *Retina reattached by gas injection* |
|---|---|---|
| Adequate | 7 | 7 |
| Inadequate | 4 | 0 |

Fisher exact probability test: $p=0{\cdot}206$, $p<0{\cdot}01$.

rapidly developed PVR (day 2 in patient 8 and days 2–3 in patient 10) over the following two-week period. Three patients had the retina reattached by surgical revision. In patient 8 the retina failed to become reattached despite two further procedures.

## Discussion

Intravitreal gas injection is an established method of retinal tamponade. The high surface tension at a gas-fluid interface can seal a retinal break, thereby allowing SRF to become actively resorbed by retinal pigment epithelium action. The buoyant force of the gas bubble may also push SRF out through the break into the vitreous.[5]

We chose 100% SF6 as the injection gas for the following reasons. An injected volume of 0·6 ml rarely causes occlusion of the central retinal artery and expands to 1·2 ml, which will tamponade approximately 70° of retina.[6] This is sufficient for most situations. In one case in this series a 1·2 ml bubble (estimated size) was used to tamponade several breaks over an arc greater than the bubble contact by progressive positioning of the patient to tamponade and reattach each break in turn. The 10–14-day life span of an SF6 bubble is in excess of the time required for chorioretinal adhesion.[7] As alternatives to SF6, both air and perfluorocarbon gases have drawbacks. Air requires a relatively large injected volume and has an insufficient longevity. Perfluorocarbon gases have the advantage of requiring only a small injected volume but the disadvantages of excessive longevity and cataractogenesis.[8]

In a large series of cases one might expect to see the same range and frequency of complications as is encountered with pneumatic retinopexy.[9] In this study no complications were encountered with the seven patients fulfilling all three criteria. However, PVR occurred in two out of four patients who were unsuccessfully given supplemental gas injection in the presence of an inadequate scleral indent.

The use of intravitreal gas to reattach the retina after early failure of scleral buckling surgery provides a simple alternative to surgical revision. It is important to assess the suitability of a particular case. Only eyes with clearly documented reappearance or increase of SRF should be considered for supplemental gas injection. This avoids the treatment of cases in which the retina may spontaneously reattach with time. The adequacy of the scleral indent must be carefully assessed before treatment. If the scleral indent is correctly placed, success is likely. If the scleral indent is inadequate, surgical revision is indicated, and supplemental gas injection should be avoided.

We thank Mr A Hughes, of the Department of Community Health, University of Bristol, for statistical analysis.

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# Reappraisal of the ratio of disc to macula/disc diameter in optic nerve hypoplasia

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**Abstract**

**The ratio of disc to macula/disc diameter is characteristically increased in eyes with optic nerve hypoplasia. We present the largest reported series of patients with a definitive diagnosis of optic nerve hypoplasia for whom this ratio has been determined. All measurements were made by an independent masked observer. Our results are in accordance with previous reports. A ratio of 2·94 provides a one-tailed upper population limit of 95%. An attempt has been made to correlate optic disc size and visual acuity. In 75% of bilateral cases the eye with the relatively smaller optic disc was found to have a better Snellen visual acuity than the fellow eye. This suggests that additional pathogenic mechanism(s) may have determined the eventual visual outcome in such eyes. Such mechanisms include macular hypoplasia, high refractive error, refractive amblyopia, central scotoma, and optic atrophy.**

Underdevelopment of one or both optic nerves is a common anomaly.[1] The aetiology is unknown. Optic nerve hypoplasia (ONH) is a diagnosis which should be considered in any person with poor vision for which there is no immediately apparent explanation. Although the small optic disc of ONH is easily detected in severe cases, more subtle forms of the disorder may present more difficulty. The differential diagnosis includes the apparently small optic nerve head of hypermetropia. Subtle forms of the disorder may be difficult to distinguish from normal appearances. Red-free fundus photography can aid in this differentiation by detecting evidence of nerve fibre layer defects which correspond with that of the pattern of visual field loss.[2] However, many cases of ONH do not show such focal defects and are manifest solely as a uniformly thin nerve fibre layer within affected areas, which makes the condition more difficult to define than focal defects.[3]

Franceschetti and Bock[4] measured the optic disc diameter by means of focal illumination of the fundus, using contact lens biomicroscopy and a micrometer scale. Estimation of the size of the optic disc by comparing the slit beam width on the Hagg-Streit 900 slit-lamp with the optic disc diameter on contact lens biomicroscopy has also been advocated.[5] These relative measurements are useful in comparing the diameter of the optic disc relative to the slit-lamp beam or the scale, because their magnification when projected on the optic disc is assumed to be the same as the magnification of the optic disc, as the slit beam and microscope optics are parfocal and both pass through the optical system of the eye.

Other methods which have been described include comparison of the size of the optic disc with the size of the whole area of the fundus as seen in the standard fundus photograph,[6] measurement with a scale over the frontal lens during indirect ophthalmoscopy,[7] direct measurements of the orbital part of the optic nerve by CT scanning,[8] A-scan ultrasonography,[8] and B-scan ultrasonography.[9]

Variations in the size of the eye with concomitant differences in dioptric power even in emmetropic eyes render absolute measurement of intraocular structures difficult.[10 11] Interference fringes provide a means of accurate measurement[12] but necessitate sophisticated equipment and a co-operative patient. The alternative is to make relative measurements from fundus photographs. The apparent size of the optic disc in fundus photographs is influenced by several factors, including the axial length, corneal curvature, and the shape of the fundus,[13] and by refractive errors and optical aberrations, but because all photographed structures are equally influenced by anatomical and refractive variation such ratios are informative. Thus comparison of the optic disc diameter (DD) with the distance between the disc and macula (D-M) provides a useful index (D-M/DD ratio) of optic nerve head size. This assumes that the paired parameters normally bear a constant relation to each other. ONH has been said to be characterised by a ratio greater than 3:1.[14–16]

We have carried out a detailed study on patients with ONH[17 18] and report our findings on the sensitivity of this technique employing the D-M/DD ratio on a cohort of patients with this condition.

## Patients and methods

### PATIENTS

The sources of patients were as follows: (1) The in-patient disease index of the Royal Hospital for Sick Children (RHSC), Glasgow; (2) the RHSC outpatient department diagnostic index maintained by the consultant staff; (3) Aberdeen Royal Infirmary, Scotland (with permission of the head of the department); (4) newly presenting cases (two patients with ONH and two with segmental ONH).

The patients thus identified were requested to attend for review. The unaided and corrected visual acuities were tested, and cycloplegic retinoscopy (half an hour after instilling 1% cyclopentolate eyedrops) was performed. The visual acuities were retested with correction whenever required. The D-M/DD ratio was identified according to the protocol outlined below. All eyes with non-segmental ONH had

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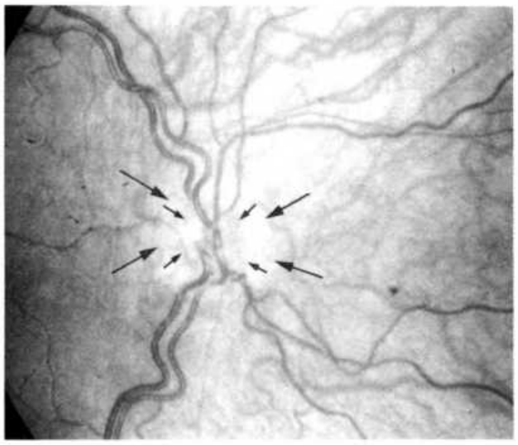

*Figure 1 The appearance of the optic disc in ONH. The 'double ring' sign is demonstrated. An inner ring represents the borders of the optic disc (arrow), and an outer ring represents the outer border of the glial tissue.*

subnormal uncorrected visual acuities. The 'double ring' sign, which is well described in the ophthalmic literature,[8,19,20] was present in all eyes (Fig 1), except in the two eyes of patient 6. However, this patient had constriction of the visual fields to 5° from fixation, mental retardation, cerebral palsy, and hypothalamic dysfunction.

### CONTROL SUBJECTS

Eighteen normal school children from a local school were tested after permission from the health authorities had been sought and consent of the parents had been obtained. All 18 children attended the clinic and together with three adult volunteers underwent visual acuity assessment, retinoscopy, and fundus photography according to the same protocol as the patients. The ages of the normal subjects ranged from 4 to 35 years (median 9, mean 10·47).

### FUNDUS PHOTOGRAPHY

All patients and control subjects underwent bilateral fundus photography. One drop of 1% cyclopentolate eyedrops was used to dilate the pupils. Both colour and red-free photographs were taken in order to facilitate identification of the optic disc boundaries and foveal position in difficult cases. Two colour (64 ASA Kodak Ektachrome) and two red-free colour fundus photographs (400 ASA Kodak Ektachrome) were taken with the same fundus camera (Canon CF-60 Z) at the 40° setting, and the clearest photographs were evaluated. In two cases (patients 6 and 20) 35° red-free fundus photography had been taken in Aberdeen Royal Infirmary (this does not, however, affect the determination of the D-M/DD ratio from these fundus photographs – see below).

*Table 1 Relationship of the visual acuity to the D-M/DD ratio in the patient group*

| | | | *Unaided VA* | | *Aided VA* | | *D-M/DD ratio* | |
|---|---|---|---|---|---|---|---|---|
| *Patient* | *Age* | *Sex* | *OD* | *OS* | *OD* | *OS* | *OD* | *OS* |
| 1 | 4 | M | 0·5/60 | 3/60 | 0·5/60 | 3/60 | 3·23 | 4·00 |
| 2 | 4 | F | 6/18 | 6/12 | 6/18 | 6/12 | 3·04 | ? |
| 3 | 8 | M | 1·5/60 | 6/36 | 1·5/60 | 6/36 | 6·08 | 4·60 |
| 4 | 17 | M | 6/60 | 6/60 | 6/60 | 6/24 | 3·26 | 3·61 |
| 5 | 21 | F | * | * | * | * | 3·44 | 3·85 |
| 6 | 19 | F | 6/60 | 5/60 | 6/24 | 6/18 | 4·08 | 4·24 |
| 7 | 11 | M | 3/60 | 6/60 | 6/60 | 6/36 | ? | 3·67 |
| 8 | 3 | M | * | * | * | * | 3·45 | 3·53 |
| 9 | 2 | M | 1/60 | 6/9 | 1/60 | 6/9 | 3·87 | ? |
| 10 | 15 | F | 6/36 | 6/18 | 6/18 | 6/12 | ? | 4·40 |
| 11 | 16 | M | 6/9 | 6/24 | 6/7·5 | 6/12 | 2·80 | ? |
| 12 | 6 | M | 3/60 | 6/60 | 3/60 | 6/60 | 3·32 | 3·67 |
| 13 | 14 | M | 6/60 | 6/36 | 6/60 | 6/36 | 2·91 | 3·58 |
| 14 | 7 | M | 6/36 | 6/60 | 6/36 | 6/60 | ? | 3·48 |
| 15 | 7 | M | 3/60 | 1·5/60 | 3/60 | 1·5/60 | ? | 3·26 |
| 16 | 26 | F | 6/7·5 | 6/7·5 | 6/6 | 6/6 | 2·68 | 3·14 |
| 17 | 4 | M | 6/60 | 6/36 | 6/60 | 6/36 | 3·44 | 3·28 |
| 18 | 19 | M | 6/12 | 6/7·5 | 6/7·5 | 6/6 | 3·22 | 3·32 |
| 19 | 4 | M | 6/12 | 6/18 | 6/12 | 6/12 | 3·47 | 3·10 |
| 20 | 43 | F | † | 6/18 | † | 6/12 | ? | 3·06 |
| 21‡ | 9 | F | 6/6 | 6/6† | 6/6 | 6/6† | 3·33 | 2·72 |
| 22‡ | 22 | F | 6/7·5 | 6/6† | 6/6 | 6/6† | 3·27 | 2·71 |

*Blind eyes. †Eyes deemed to have no ONH. ‡Patients with unilateral right segmental ONH. ?=Not available. VA=visual acuity.

### IMAGE ANALYSIS

Fundus photographs were assessed by the VIDS V image analysis system (Analytic Measuring Systems Ltd). In every case the average disc diameter was calculated by adding the vertical and transverse disc diameters and then dividing by 2. The distance from the temporal margin of the optic disc to the fovea was measured from each photograph for both groups of subjects. Half the average diameter of the optic disc was added to this distance to obtain the 'disc-macula distance'. The disc-macula/disc diameter (D-M/DD) ratio was calculated for all patients and normal subjects. The same calibration technique was used for all the photographs studied. All the readings were taken and analysed separately by a masked independent observer (GND). The slides of the patients and of the normal control subjects had been mixed at random before they were analysed.

### VISUAL ACUITY

The Snellen chart was used to test both the uncorrected and corrected visual acuities at a distance of 6 metres. The luminance of the Snellen test type was measured by a Solex SL 100 Lux meter; the mean screen luminance of six readings was 2900 asb. When young age or mental retardation resulted in inability to read the Snellen characters, the identity of the letters was sought by asking the subject to point to corresponding letters on a hand held Sheridan-Gardiner test form.

## Results

Fundus photographs were taken for both eyes of 21 normal subjects by the same protocol. It was possible to determine the D-M/DD ratio for 40 eyes of 21 normal subjects. It was also possible to perform fundus photography in 41 eyes of 23 patients, including two patients with segmental ONH. However, in two eyes the quality of the photographs was poor, in two other eyes the fovea was not included in the fundus photographs, and in a further three eyes the fovea could not be located. Therefore measurements could be made to provide the D-M/DD ratio for 34 eyes of 22 patients (Table 1).

The mean D-M/DD ratio for the two eyes was taken as the datum value for a subject unless only one eye had been assessed, in which case the value for that eye was taken. The rationale for this type of analysis has been described previously.[21,22]

The mean D-M/DD ratio for the normal

*Table 2 Refractive errors of patients (reproduced with permission from the British Journal of Ophthalmology 1990; 74: 297–9)*

| | TSP | | Astigmatism* | |
|---|---|---|---|---|
| Patients | OD | OS | OD | OS |
| 1 | 1·62 | 1·12 | 0·25 | 0·75 |
| 2 | 3·12 | 3·12 | 0·25 | 0·25 |
| 3 | 2·00 | 2·12 | 0·5 | 1·75 |
| 4 | −2·25 | −0·87 | 6 | 3·25 |
| 5 | 0·12 | 0·00 | 1·75 | 1·5 |
| 6 | 1·37 | 2·62 | 0·75 | 2·75 |
| 7 | 1·25 | 1·12 | 4·00 | 4·25 |
| 8 | 1·62 | 0·5 | 1·25 | 1·5 |
| 9 | 2·25 | 2·12 | 0·5 | 0·25 |
| 10 | −1·37 | −1·37 | 4·25 | 4·25 |
| 11 | 1·25 | 0·75 | 0·5 | 0·5 |
| 12 | 1·12 | 2·37 | 2·75 | 2·25 |
| 13 | 0·5 | 0·37 | 2·5 | 2·25 |
| 14 | 1·5 | 2·5 | 1·5 | 2·5 |
| 15 | 0·25 | −2·25 | 1·25 | 2·25 |
| 16 | 1·75 | 1·75 | 0·5 | 0·5 |
| 17 | 4·5 | 5·00 | 0·5 | 1·00 |
| 18 | 1·5 | 2·37 | 0·5 | 0·25 |
| 19 | 2·00 | 2·62 | 1·00 | 1·75 |
| 20 | † | 0·5 | † | 0·5 |
| 21*‡ | 3·00 | 3·00† | 0·00 | 0·00 |
| 22*‡ | 1·75 | 1·75† | 0·00 | 0·00 |

*In dioptres. †Eyes deemed to have no ONH.
‡Patients with segmental ONH. TSP=total spherical power.

group was 2·62. The mean ratio for the patient group was 3·57. As the data were found to be not normally distributed, an upper limit for the normal range was estimated by direct calculation of percentiles.[23] In view of the relatively small number of control subjects the most extreme limit which could be calculated was the 95% one-tailed upper population limit, which was 2·94. For only one patient (No. 11, who had bilateral ONH, but for whom only the right eye could be photographed) was the D-M/DD within this 95% limit for normal subjects; his D-M/DD ratio was 2·80. However, this patient showed the double ring sign in both eyes, and his corrected visual acuities were OD 6/7·5 and OS 6/12.

We looked at the visual acuity of the better eye in 12 patients with bilateral ONH for whom fundus photographs were available (blind eyes and eyes with segmental ONH were excluded) (Table 1). The visual acuities were compared with the D-M/DD ratios. No significant correlation was found (Pearson correlation coefficient, $p>0·1$). Furthermore, in the eight patients with bilateral ONH for whom the D-M/DD ratio was calculated for both eyes, and for whom the visual acuities of the two eyes were different (patients 1, 3, 4, 6, 12, 13, 17, 18) six patients (75% were identified in whom the eye with the better visual acuity had a relatively larger D-M/DD ratio than the worse eye (Table 1).

It is of interest that in 12 of 15 patients (80%) in this series, with bilateral ONH and asymmetrical corrected visual acuities, the left eye was the better eye. It is also noteworthy that for 10 out of 12 (83%) of the patients with bilateral ONH for whom the D-M/DD ratio could be determined for both eyes there was more astigmatism in the eye with the smaller D-M/DD ratio (the eye with the relatively larger optic disc) (Table 2). In only one patient was the degree of astigmatism less in the eye with the smaller ratio, and in one patient there was an equal degree of astigmatism of 0·5 dioptre in both eyes. This has been reported in detail elsewhere.[17]

Six patients (4, 6, 7, 10, 12, 13) had bilateral asymmetrical ONH with a significant refractive error in the eye which had the smaller D-M/DD ratio. The visual acuities both with and without correction were the same in the eye with the better visual acuity for two of these patients (12 and 13). Visual acuities were improved with correction by more than one Snellen line in only two patients.

As for the two patients with segmental ONH, although the D-M/DD ratios for the affected eyes were significantly higher than for the normal fellow eyes, there was no impairment of visual acuity and no associated refractive error.

## Discussion

The D-M/DD ratio is the ratio of the horizontal distance between the centre of the optic disc and the macula to the mean diameter of the optic disc, as evaluated from fundus photographs. This study presents the largest series of patients with ONH in whom this ratio has been measured. The second largest series comprised 19 eyes of 11 patients with ONH.[15]

The 95% one-tailed upper population limit of the D-M/DD ratio for the normal group in this study was 2·94. This indicates that in practice a ratio of 3 or more provides reliable supportive evidence for the diagnosis of ONH, and accords with previous reports.[14–16] Awan[14] selected the horizontal meridian only as an index for the disc diameter. Both Awan[14] and Wakakura and Alvarez[15] added half the transverse diameter of the optic disc to the distance between the fovea centralis and the temporal margin of the optic disc in order to calculate the disc-macula distance.

The pupils of only one patient (who was blind; no. 5) did not react to light. This absence of the pupillary light reaction indicates severe involvement of the light sensitive ganglion cells and the 'pupillary' fibres in the optic nerve as well as all the other ganglion cells, as this patient had no light perception in either eye.

The small size of the optic disc must be associated with the visual deficit in these patients. The following findings that indicate that additional factor(s) must contribute to the eventual visual outcome: (1) the visual acuities and the D-M/DD ratios were not significantly correlated in patients with bilateral ONH; (2) 75% of patients with assymmetrical bilateral ONH had a better visual acuity in the eye with the relatively larger D-M/DD ratio. Such factors may include the following.

*Macular hypoplasia.* In three eyes for which the photographs had been correctly exposed the position of the fovea could not be discerned in any of the fundus photographs, which therefore excluded them from further study. The visual acuities in these three eyes were hand movement in two and counting fingers in one. This suggests a degree of macular hypoplasia in these eyes, which may comprise features other than isolated absence of ganglion cells in the macula and their nerve fibres. Macular hypoplasia has not hitherto been described in association with ONH. However, histopathological study would be required to validate this hypothesis. In the two histopathological reports for patients blind with

ONH total absence of the ganglion cells and the nerve fibre layer has been documented in the affected retinae, but no comments were made on macular morphology.[24 25]

*Central scotoma.* It was not possible to assess the visual fields in any of the patients who had poor corrected visual acuities. For one patient (no. 4) visuscopy indicated that an area temporal to the macula was employed for fixation by each eye. Both of these eyes had uncorrectable visual acuities despite high refractive errors. It is likely that in this patient eccentric fixation may have been caused by large central scotomata, perhaps due to underdevelopment of ganglion cells of the macula.

*Refractive errors and refractive amblyopia.* Refractive errors have recently been reported in association with ONH.[17] In patients 7 and 10 there were high refractive errors in the better eyes, but the better eye of each of these patients improved by only one Snellen line by correction. An element of refractive amblyopia may therefore have contributed to impaired visual function in these two patients.

*Optic atrophy.* Optic atrophy and ONH are both manifestations of an 'insult' to the developing optic nerve. Therefore it is possible that the pale colour of the optic disc commonly seen in ONH is not due to a relative increase in the proportion of glial tissue (which is believed not to be affected in ONH), but is due to an absolute increase of the glial tissue and diminished vasculature in these optic nerves due to concomitant optic atrophy.

In conclusion, we recommend application of the D-M/DD ratio to assist in confirming the diagnosis of ONH. Simple measurements from fundus photographs are easy to carry out. In a child with bilateral ONH conclusions on the visual potential for an eye should not be drawn from the appearance of the optic disc alone. The diagnosis of ONH necessitates careful retinoscopy not only to exclude hypermetropia, but also to exclude associated astigmatic refractive errors in such patients, so that their visual development may be optimised.

Further research is required to explain the observation that several patients with ONH had no significant improvement in their visual acuities despite correction of high refractive errors. Further research is also required into concomitant mechanisms, other than the optic nerve size, which may impair the eventual visual outcome in some patients with bilateral ONH.

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# Double-masked trial of topical acyclovir and steroids in the treatment of herpes zoster ocular inflammation

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## Abstract

**Ninety seven new patients with ophthalmic zoster were randomly allocated to three topical treatment groups: acyclovir (ACV) ointment and placebo drops (AP), placebo ointment with steroid drops (PS), and acyclovir ointment with steroid drops (AS). The dosage administered was determined by the score of the ocular inflammation. Follow-up was for at least one year. The results showed that topical ACV alone is insufficient for severe ocular inflammation but is not inclined to lead to recurrences in milder cases. Topical steroid alone is effective but tends to necessitate prolonged treatment. Combined steroid and ACV is questionably better than steroid alone and causes marginally fewer rebound inflammations.**

Ophthalmic zoster has been said to give rise to ocular complications in 50% of patients.[1] These are chiefly inflammatory and range from being mild, such as episcleritis, to severe, such as sclerokeratitis and hypertensive iritis. The mechanisms of these complications are poorly understood but clearly involve replication of the varicella/zoster virus in the early stages and then the inflammatory response. The latter is conventionally treated with topical steroid,[2] which, though usually effective, may have to be continued for long periods, as inflammation tends to reappear during or shortly after withdrawal.

On the other hand, viral replication may be limited early on by acycloguanosine (acyclovir or ACV), a potent and selective inhibitor of viruses of the herpes group, in particular herpes simplex virus types 1 and 2 and to a less extent varicella-zoster virus (VZV).[3,4] The intraocular penetration of topical ACV is superior to that of other antiviral agents[5] and would therefore make it the rational choice. An open study of topical acyclovir on 18 patients with a short follow-up[6] showed it controlled keratoconjunctivitis in 15 of the patients without topical steroid, and there was no recurrence on stopping treatment. A further study comparing topical ACV and steroid reported ACV to be superior to steroid in terms of the median healing time of corneal epithelial ulcers, but there was no significant difference for stromal lesions, uveitis, or scleritis.[7] Of the patients on steroid 63% had a recurrence of ocular inflammation during or after withdrawal of therapy, making the mean treatment time in the steroid treated group significantly longer than in the ACV group.

These results did not correspond with our experience of ACV at Moorfields,[8] where half of our patients, despite being treated early with it, developed very serious ocular inflammation necessitating and responding well to topical steroids (admittedly with attendant liability to relapse). Moreover, in our experience mild disease such as corneal microdendritic ulcers, some nummular keratitis, and most cases of episcleritis are self-limiting and do not require any treatment. Therefore we consider that ACV does not have any effect in these cases and steroid could be positively harmful.

The mechanisms by which rebounds in ocular disease may follow steroid withdrawal are still uncertain. Steroids can enhance viral replication[9] by the suppression of some of the inflammatory responses. It is not known whether the chronic or relapsing ocular lesions in zoster are dependent on viral replication or the presence of some sort of antigen. Perhaps it is significant that, although replicating virus is present in the acute epithelial lesions of zoster,[10] so far as we know replicating virus has not been identified or cultured in pathological specimens from chronic cases. It would therefore seem logical to try an antiviral during the acute phases of the disease but less certainly in the later phases.

The use of ACV and steroids, separately or in combination, compared with placebo in the treatment of herpes zoster ocular inflammation has not previously been examined in a controlled clinical trial. We considered the large number of patients we see and the doubts raised by our observations justified such a three-armed double blind trial.

## Patients and methods

New patients presenting at Moorfields Eye Hospital with ophthalmic zoster were offered inclusion in the trial. Patients excluded were those who did not give their consent, were unwilling or unable to attend regularly for clinical assessment, were under 18 years, had received antivirals or steroid by any route, had other significant ocular pathology, had no eye disease at all, and had had the onset of the rash over 3 weeks previously.

Patients willing to take part were informed of the nature of the trial and gave their written consent.

The trial was double masked and randomised. Patients eligible for entry were randomly allocated to receive either acyclovir ophthalmic ointment and placebo eye drops (AP), placebo ointment and steroid eye drops (PS), or acyclovir ophthalmic ointment and steroid eye drops (AS).

On admission to the trial the following details were recorded: time from onset of rash, preceding ocular therapy, other eye disease, previous glaucoma or family history of glaucoma, and whether eye involvement was mild, moderate, or severe.

*Table 1 Score card for recording inflammatory index*

| *Visit (weeks)* | *1st* | *2nd* | *3rd* | *4th* | *8th* | *12th* | *16th* | *20th* | *26th* | *52nd* |
|---|---|---|---|---|---|---|---|---|---|---|
| Date | | | | | | | | | | |
| conjunctivitis<br>(0 1 2 3) | | | | | | | | | | |
| episcleritis<br>(0 2 4 6)<br>(sectors 1 2 3) | | | | | | | | | | |
| scleritis<br>(0 4 8 12)<br>(sectors 1 2 3) | | | | | | | | | | |
| nummular keratitis<br>(0 2 4 6)<br>(sectors 1 2 3) | | | | | | | | | | |
| disciform<br>(0 2 4 6)<br>(sectors 1 2 3) | | | | | | | | | | |
| sclerokeratitis<br>(0 2 4 6)<br>(sectors 1 2 3) | | | | | | | | | | |
| mucous plaque<br>(0 2 4 6)<br>(sectors 1 2 3) | | | | | | | | | | |
| corneal oedema<br>(0 4 8 12) | | | | | | | | | | |
| iritis<br>(0 2 4 6) | | | | | | | | | | |
| visual acuity | | | | | | | | | | |
| applanation | | | | | | | | | | |
| Score | | | | | | | | | | |
| Potency | | | | | | | | | | |

*Table 2 Dosage regimen*

| *Log dilution of drop* | *Ointment frequency* | *Score* | *Potency* |
|---|---|---|---|
| 0·1% ×6/day | ×5 | 13+ | 1 |
| 0·1% ×4/day | ×4 | 11–12 | 2 |
| 0·1% ×3/day | ×3 | 9–10 | 3 |
| 0·03%×3/day | ×3 | 7–8 | 4 |
| 0·01%×3/day | ×3 | 5–6 | 5 |
| 0·01%×2/day | Nil | 3–4 | 6 |
| 0·01%×1/day | Nil | 1–2 | 7 |

A scoring system of the degree of inflammation of the eye was devised in order to calculate the intensity of treatment to be used. In essence each inflammatory lesion was scored as follows: no lesion (0), mild (1), moderate (2), and severe (3), and all scores were added together to reach a total. However, we considered from clinical experience that this basic scoring system was inadequate alone to indicate appropriate intensity of treatment, particularly with reference to steroids. This is because lesions are often multifocal in several sectors, and certain inflammatory conditions require high doses of topical steroid to control them. For instance, conjunctivitis is a very mild and transient condition responding readily to a low dose of steroid, whereas scleritis and corneal oedema are severe and require intensive topical steroid to control them. There are other conditions of intermediate severity such as episcleritis and nummular keratitis. We therefore modified the scoring to bring it into line with the most appropriate intensity of treatment and thus quadrupled the score of scleritis and doubled that of the intermediate group. We also added a score of 1 for one sector, 2 for two sectors, and 3 for more than two sectors. Table 1 shows the inflammatory score sheet where the inflammatory indices of the ocular complications were recorded and totalled.

Table 2 gives the therapeutic regimen based on these different scores. All patients with scores over 16 had the most intensive treatment possible, and at each visit the scores were reassessed and the dosage adjusted accordingly. When the score fell below 5 ointment was stopped. This was because Wellcome considered that ACV became relatively ineffective at doses less than three times a day. The drops, however, were continued because even minute doses of steroid appear to have a therapeutic effect. Once signs of active ocular inflammation had ceased, treatment was continued at the minimum dose for at least three months and halved after that for a further two months to cover any rebound phenomenon.

A 1 cm ribbon of 3% acyclovir ointment or placebo was administered on to the lower tarsal conjunctiva. Dilutions of dexamethasone drops at 0·1%, 0·03%, and 0·01% were prepared with matching placebo. One drop was instilled at a time. ACV ointment and matching placebo were packaged and labelled by Wellcome. The placebo consisted of the same ingredients as the drug formulation, without the ACV. Steroid eye drops and matching placebo were prepared and labelled by the pharmacy at Moorfields Eye Hospital. The placebo consisted of the diluent used in the preparation of the steroid drops and was labelled 0·1%, 0·03%, and 0·01%.

Patients were seen as often as clinically necessary but at least twice in the first week of presentation, weekly thereafter until the end of the first month, and then at monthly intervals intil the end of therapy. The clinical proformas and score sheets were completed on each occasion, the total inflammatory score calculated, and the appropriate treatment administered. Any adverse symptoms or signs potentially attributable to the therapy were carefully documented in the adverse reactions chart. Final assessments were made at six and 12 months following resolution of active ocular involvement.

Patients were withdrawn from the trial if signs of toxicity or side effects developed, if they deviated seriously from the protocol, or if their ocular complications progressed despite full therapy (potency 1). The last was taken as when the ocular inflammatory score continued to rise over a three-day period or more on full therapy. Then the patient was placed on full strength dexamethasone at least six times a day to prevent any scarring of the eye. We continued to monitor all patients withdrawn from the trial.

Any recurrence of ocular complications

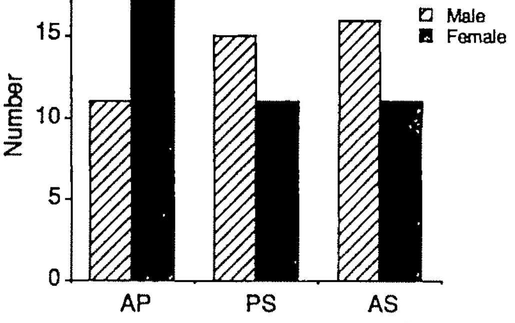

*Figure 1 Sex distribution of the patients in the three groups.*

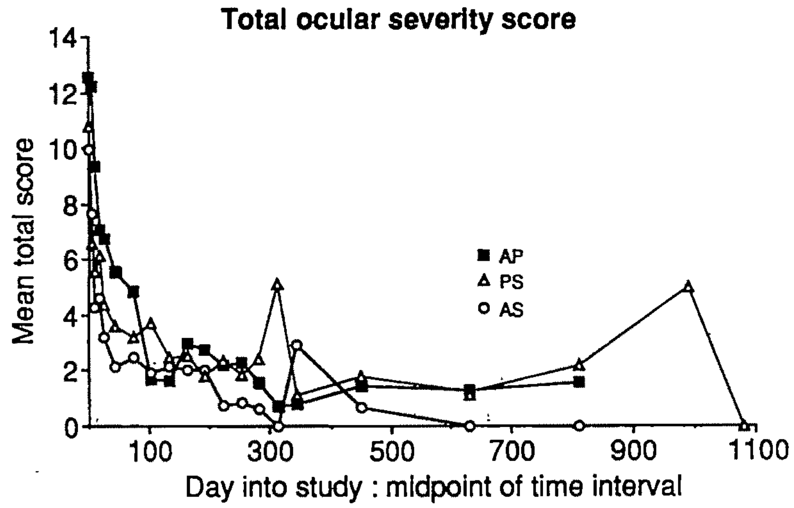

*Figure 2 Severity of ocular inflammation plotted against time in the three groups.*

*Table 4 Time in days to resolution of ocular inflammation in those patients who healed (expressed as a mean)*

| | *AP*<br>*ACV/placebo* | *PS*<br>*Placebo/steroid* | *AS*<br>*ACV/steroid* |
|---|---|---|---|
| Conjunctivitis | 23·9<br>(24·4)* | 26·2<br>(33·4) | 20·5<br>(24·6) |
| Episcleritis | 127<br>(94·8) | 85·9<br>(101·3) | 67·9<br>(74·9) |
| Keratitis | | | |
| nummular | 153<br>(199·7) | 136·5<br>(24·8) | 66·6<br>(72·8) |
| disciform | 14·0<br>(0) | 63·0<br>(0) | 18<br>(0) |
| sclero | 7<br>(0) | 6<br>(0) | 124–5<br>(150·6) |
| mucous plaque | 6<br>(1·4) | 0<br>(0) | 7<br>(0) |
| oedema | 6·5<br>(2·3) | 35·2<br>(68·7) | 7<br>(4) |
| Iritis | 91·9<br>(99·5) | 55·5<br>(72·6) | 42·5<br>(62·1) |

*SD in parentheses.

during the period in which the frequency of administration of the treatment was being reduced was treated in accordance with the inflammatory scoring and the drug dosage appropriately increased. Any recurrence that occurred after the end of therapy was treated similarly.

## Results

The original intention was to recruit 120 patients, but this proved impracticable. The main reason was that in the later stages of the trial a large proportion of patients presenting to the Accident and Emergency Department had already been started on some form of ACV by their general practitioners. This made recruitment increasingly slow and those recruited increasingly unrepresentative. It was therefore decided to limit the numbers to 97. Of these, 14 sets of results could not be used because of inadequate documentation or follow-up; 30 patients remained in the ACV/placebo (AP) group, 26 in the steroid/placebo (PS) group, and 27 in the ACV/steroid (AS) group.

*Table 3 Ocular inflammatory complications in patients with ophthalmic zoster treated with topical acyclovir and placebo, topical steroid and placebo, topical steroid and acyclovir*

| | *AP*<br>*ACV/placebo*<br>*(30 patients)* | *PS*<br>*Placebo/steroid*<br>*(26 patients)* | *AS*<br>*ACV/steroid*<br>*(27 patients)* |
|---|---|---|---|
| Conjunctivitis | | | |
| present at entry | 27 | 24 | 26 |
| mean baseline score | 1·7 | 1·5 | 1·5 |
| Episcleritis | | | |
| present at entry | 29 | 26 | 27 |
| mean baseline score | 3·2 | 2·9 | 2·9 |
| mean no. of sectors | 2·7 | 2·5 | 2·3 |
| Nummular keratitis | | | |
| present at entry | 7 | 5 | 6 |
| mean baseline score | 0·7 | 0·5 | 0·3 |
| mean no. of sectors | 0·4 | 0·2 | 0·3 |
| Disciform keratitis | | | |
| present at entry | 1 | 1 | 1 |
| mean baseline score | 0·1 | 0·2 | 0·1 |
| mean no. of sectors | 0·03 | 0·1 | 0·1 |
| Sclerokeratitis | | | |
| present at entry | 1 | 1 | 2 |
| mean baseline score | 0·1 | 0·1 | 0·2 |
| mean no. of sectors | 0·03 | 0·1 | 0·1 |
| Mucous plaque keratitis | | | |
| present at entry | 2 | 0 | 2 |
| mean baseline score | 0·1 | 0 | 0·1 |
| mean no. of sectors | 0·1 | 0 | 0·04 |
| Corneal oedema | | | |
| present at entry | 8 | 5 | 3 |
| mean baseline score | 1·5 | 0·9 | 0·7 |
| Iritis | | | |
| present at entry | 21 | 14 | 11 |
| mean baseline score | 1·9 | 1·7 | 1·0 |

The sex distribution was significantly different between the groups (Fig 1), but we did not consider this had any relevance to the trial. A significant difference in severity of initial disease was noted, with the rounded mean initial clinical scores for the AP, PS, and AS groups being 13, 11, and 10 respectively (Fig 2). Analysis shows that these scores were not strictly random. There was a bias towards more severe initial disease in the AP group because of a higher preponderance of severe uveitis and corneal oedema and towards less severe complications in the AS one.

There were no significant differences between the groups in terms of distribution of ocular complications (Table 3). For the more infrequent problems there would have been insufficient numbers.

Rates of healing are shown in Table 4. The rate was significantly poorer for episcleritis in group AP, whereas group AS showed faster resolution of inflammation overall, though the rate of severe complications was too low for any differences to be detected.

Table 5 gives the overall resolution of ocular inflammation. Treatment failure, that is when the full intensity of trial drug combinations failed to control inflammation, occurred in 12 out of 30 AP, two out of 26 PS, and three out of 27 AS ($\chi^2$ test, $p<0\cdot01$). In those patients whose condition failed to settle down it responded to intensive topical steroid and did not present any significant management problems.

Recurrences, either during tail-off or after stopping treatment, occurred in 3/16 AP, 7/22 SP, and 9/26 AS. The denominator is those who did not fail to respond to treatment ($\chi^2$ test, $p>0\cdot05$). Treatment duration was over one year in 3/16 AP, 8/24 AS, and 3/24 AS. However, it should be noted that as 12 of the AP group were withdrawn because of treatment failure the

*Table 5 Overall resolution of ocular inflammation*

| | *AP*<br>*ACV/placebo* | *PS*<br>*Placebo/steroid* | *AS*<br>*ACV/steroid* |
|---|---|---|---|
| Healed | 13 | 21 | 24 |
| Not healed | 17 | 4 | 2 |
| Unknown | 0 | 1 | 1 |

milder ocular complications tended to remain in this group. Therefore there would be less tendency to relapses among them.

No difficulties were experienced with drop allergies, steroid induced rise of intraocular pressure, or other drug side effects.

## Discussion

At their face value these results indicate that topical ACV alone is insufficient for severe ocular inflammation, takes longer to settle milder inflammation, but is not inclined to lead to recurrences in the milder cases. The results of the AP group would suggest that some acute ocular inflammations such as mild episcleritis and nummular keratitis are self limiting. Topical steroid alone is effective but prone to lead to prolonged treatment; whether it worsens ocular complications is not possible to say from these data. The combined ACV and steroid group is questionably better than the steroid alone in the short term and has a reduced number of patients with rebound inflammation, but this is not statistically significant. Interpretation of this trial is made difficult by the obvious initial differences between the groups. However, we have been assured by our statisticians that they do not account for the whole difference, and qualitatively the results are useful.

Having demonstrated the relative ineffectiveness of the topical ACV preparation there remain the systemic preparations which achieve better tissue concentrations. Controlled clinical trials have shown that ACV, given intravenously, significantly shortens the course of acute zoster skin rash, especially in immunosuppressed patients.[4 11] It is also claimed that given orally at 600 and 800 mg five times a day for 8–10 days at the start of the disease it significantly reduces the occurrence of ocular complications[12] and postherpetic neuralgia.[13] However, it must be said that the reported reduction of ocular complications is based on one multicentre trial with exclusion of cases with significant ocular inflammation at presentation, and the reduction of postherpetic neuralgia is a contentious issue depending on the definition of postherpetic neuralgia as opposed to acute neuralgia and on the normal incidence of neuralgia.[14] Perhaps the next step is a three-armed clinical trial to decide whether a 10-day course of full dose oral ACV early on is more effective in reducing ocular inflammation than a placebo and systemic steroid. It should of course be borne in mind that the routine use of a systemic course of ACV has financial implications for health services.

It is at first sight surprising that antivirals are not more effective in zoster. The ocular complications of zoster presumably stem from the presence of VZV, which initially is replicating, and the inflammatory response. Treatment can be directed to both components. The main difficulty is with timing and deciding which component is more significant. Another problem is gaining access to patients in the early stages of the disease. Unfortunately, chronic ocular inflammation may continue for years in some cases and is presumably not dependent on the presence of virus as we know it. Perhaps the virus at its active stage causes an antigenic change in the damaged tissues and remains there not replicating in an altered form, unidentifiable with conventional electron microscopy or culturing. So at a late stage of presentation (often the case) one would not expect conventional antivirals to work. Steroids on the other hand will suppress the inflammatory response causing tissue scarring at any stage and may be necessary in the long term if the antigenic stimulus continues. The latter would explain the difficulty in withdrawing the drug as opposed to steroids promoting survival of live virus in the tissues. The other disadvantages of steroid (glaucoma, cataract, and superinfections) should of course be borne in mind.[2]

It would be helpful at this stage to compare and contrast HSV and VZV virus. HSV is a more aggressive virus and replication is more significant in producing overall disease events than VZV. HSV can be found replicating in the eye at all stages of the disease, whereas VZV has been cultured only at the beginning. HSV is more sensitive in vitro to ACV than VZV. This would explain the poorer response of zoster to the drug. They both share an inflammatory component in their disease process which is double-edged; modifications by steroid is necessary to prevent scarring and optimise outcome. However, whereas antiviral cover is important with HSV to prevent corneal epithelial loss and stromal thinning, it is not strictly necessary with VZV. At this stage it is not clear whether antiviral cover in chronic HSV corneal stromal disease modifies the inflammation, but the seemingly better results in the AS group in this trial suggest there may be a positive benefit, though not quantifiable in zoster keratitis. It is interesting that chronic stromal keratitis in both conditions may be exquisitely sensitive to topical steroid: even 0·03% prednisolone drops on alternate days can be enough to control a potentially severe inflammation.

The general conclusions relating to management of zoster ocular disease are that mild inflammation does not require any treatment, whereas more severe problems do. In the long term a combination of ACV and steroid in the more severe complications may be appropriate to prevent relapses.

This trial gives only a general indication for treatment and cannot give a recipe, which will depend on individual characteristics. The finer judgments require an extensive knowledge of the natural and unnatural history of viral ocular disease and close observation. There is no single best treatment.

We thank Messrs Wellcome for their cooperation in designing, analysing results and providing ACV We would especially like to thank David Grant for his help

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# FIFTY YEARS AGO

## Treatment of Mustard Gas Lesions of the Eye

*To the Editors of*
THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS—An instruction EMSI 252 (revised) on this subject has been widely distributed to the officers, consultants and hospitals of the Emergency Medical Service. It came before the Medical Board of Moorfields Eye Hospital 'for your information.' The Medical Board considered the instruction and felt that several points in it required comment.

1. The use of albucid solution is advised at First Aid Posts and at Hospitals in cases in which the eyes have been affected by gas vapour or gas splashing. It must be pointed out that the use of sulphanilamide preparations is not directed against gas contamination but only against subsequent infection of the conjunctiva and that opinion as to its efficiency in this latter respect is far from being generally favourable.

2. No mention is made in the instruction of the very diverse lesions which may be produced by gas, most of them slight and very few of them serious.

3. No indication is given of the treatment necessary when the cornea is definitely involved and while water is advised for irrigation of the eye at an incident and at First Aid Posts, no advice is given as to the lotion to be used for the irrigations recommended at Hospitals.

It would appear that this instruction is not in fact the 'result of further experience' and should be withdrawn and replaced by a carefully considered and detailed note based on actual experience obtained in the last war and on substantiated experimental evidence

We are,
Yours faithfully.
F. A. JULER.
MAURICE WHITING.

*Br J Ophthalmol* 1941; 25: 394–5

*British Journal of Ophthalmology*, 1991, 75, 547–551

# Progression of diabetic retinopathy after cataract extraction

Ayala Pollack, Shlomo Dotan, Moshe Oliver

## Abstract

**The course of diabetic retinopathy following cataract extraction was studied retrospectively in 89 patients (89 eyes). Cataract extraction was extracapsular in 12 eyes (13·5%), extracapsular with intraocular lens implantation in 37 (41·6%), and intracapsular in 40 (45%). In 55 eyes (61·8%) there was no change in the retinal status after surgery, and in 34 (38·2%) there was progression of diabetic retinopathy. In the eyes showing progression there was appearance or aggravation of non-proliferative changes in 85·3% and development of proliferative diabetic retinopathy in 14·7%. Most of these eyes (91%) deteriorated within six months of surgery. Risk factors for the progression of diabetic retinopathy were the preoperative existence of diabetic retinopathy p<0·005) and the need for antidiabetic agents in addition to dietary control in the management of diabetes (p<0·025).**

Diabetes mellitus occurs in an estimated 2·3% of the population in the United States.[1] This means that the number of diabetic patients undergoing cataract surgery every year is relatively large and is expected to increase even further with the gradual rise in life expectancy of diabetic patients owing to improved medical management.

The effect of cataract surgery on the postoperative course of diabetic retinopathy is unclear. Jaffe and Burton[2] reported the development of a severe exudative form of diabetic macular oedema following cataract extraction. We have recently described the pattern of deterioration of diabetic retinopathy after cataract surgery.[3] Other authors[4-6] have also described postoperative progression of diabetic retinopathy resulting in poor vision. In contrast, Sebestyen[7] found that cataract surgery was not associated with the progression of diabetic retinopathy, as in his series of patients similar progression was observed also in the unoperated fellow eye.

The purpose of this retrospective study was to examine the relationship between cataract surgery and the postoperative course of diabetic retinopathy.

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## Patients and methods

The records of 170 consecutive diabetic patients who underwent cataract extraction in our department between 1977 and 1986 were reviewed retrospectively. The study population comprised 89 patients who met the following criteria: (1) diabetes mellitus diagnosed at least six months prior to cataract surgery; (2) uneventful surgical procedure, with no vitreous loss or rupture of posterior lens capsule; (3) no laser treatment for established diabetic retinopathy applied either before surgery or within one month after surgery; (4) no other ocular disorders; (5) a postoperative follow-up period of at least one year; (6) a fundal examination prior to or within three days after surgery which served as a baseline examination for further comparison of the postoperative retinal course; and (7) additional fundal examinations during each of three distinct periods within the first year of follow-up. The first of these follow-up periods, F1, was from the beginning of the second week after surgery to the end of the third month. The second, F2, was between four and six months after surgery, and the third, F3, was between the seventh and the twelfth month.

For each patient a standardised medical protocol was completed, giving detailed demographic and clinical information including duration of diabetes mellitus, presence of other systemic diseases, and types of medication. The findings of the baseline ocular examination as well as those of each follow-up period were recorded. The examinations included best corrected visual acuity, applanation tonometry, biomicroscopy, Goldmann three-mirror examination, and indirect ophthalmoscopy. Also recorded were the findings of colour fundus photographs and of fluorescein angiography and the results of laser treatment applied during the follow-up periods. Laser treatment consisted of panretinal photocoagulation for proliferative or severe non-proliferative diabetic retinopathy and/or focal or grid argon green laser photocoagulation for macular oedema.[8-11]

On the basis of the ocular findings two subgroups were identified. The first, defined as the 'no change' subgroup, consisted of eyes in which the retinal status remained unchanged following surgery regardless of whether diabetic retinopathy was present preoperatively. The second, termed the 'progression' subgroup, consisted of eyes in which diabetic retinopathy progressed following surgery. Progression was considered to have occurred either when (1) a patient with *no* pre-existing diabetic retinopathy (NoDR) developed either non-proliferative (NPDR) or proliferative diabetic retinopathy (PDR) after surgery; or (2) a patient with pre-existing NPDR showed either postoperative aggravation of the non-proliferative changes or development of PDR, as we have previously described.[3]

Three surgical techniques were employed. Intracapsular cataract extraction (ICCE) was performed between 1977 and 1980, and extracapsular cataract extraction (ECCE) or extracapsular cataract extraction with intraocular lens implantation (ECCE with IOL) between 1980 and 1986. During 1979–80 there was a period of

*Table 1 Comparison of clinical features in study group and controls*

| | *Operated patients* | | | *Non-operated patients* | |
|---|---|---|---|---|---|
| | *No change (55 cases) (61·8%)* | *Progression (34 cases) (38 2%)* | *p* | *No change (61 cases) (87 2%)* | *Progression (9 cases) (12·8%)* |
| Mean age, yr (range) | 67·7, SD 8 (45–58) | 66·5, SD 7 (49–77) | | 63 1, SD 7 (45–79) | 61·4, SD 6 (45–80) |
| Mean duration of DM, yr (range) | 10 9, SD 9 (0·5–30) | 9·4, SD 6 (1·5–28) | | 10, SD 9 (0 5–30) | 11·1, SD 7 (1–30) |
| *No. of patients (%)* | | | | | |
| Male·female | 23:32 (41 58) | 16:18 (47 53) | | 24.37 (39:61) | 3 6 (33:67) |
| Management of DM. | | | | | |
| Diet alone | 12 (22) | 1 (3) | <0 025 | 5 (8) | – |
| Hypoglycaemic agents | 33 (60) | 24 (71) | | 32 (53) | 4 (44) |
| Insulin | 10 (18) | 9 (26) | | 24 (39) | 5 (56) |
| Vascular disease | | | | | |
| Hypertension | 22 (47) | 12 (40) | | 16 (26) | 5 (56) |
| Cardiac | 6 (13) | 4 (13) | | 3 (5) | 1 (11) |
| Other diseases· | 2 (3·6) | 3 (9) | | 1 (1·6) | – |

DM=diabetes mellitus

transition from the ICCE to the ECCE technique, when both procedures were used. In the earlier ECCE procedures IOL implantation was not performed because of our lack of experience with IOLs in diabetic eyes. All operations were performed by senior surgeons specialised in anterior chamber surgery. Fundal examinations, colour fundus photographs, and fluorescein angiography readings were performed by retinal specialists.

The control group consisted of 70 diabetic patients who had been admitted to our retina clinic for evaluation of their diabetic retinopathy status and were not operated on. Inclusion criteria were (1) completion of the same standardised medical protocol as the study group, described above; (2) diabetes mellitus diagnosed at least six months prior to the initial evaluation; (3) no prior laser treatment for established diabetic retinopathy; (4) no laser treatment for diabetic retinopathy performed either immediately or within one month following the initial examination; (5) no other ocular disorders; (6) a follow-up period of at least one year; and (7) at least three fundal examinations, F1, F2, F3, as described above for the study group.

The $\chi^2$ test was used for statistical analysis.

*Table 2 Postoperative progression of diabetic retinopathy in relation to the surgical technique (numbers of eyes with percentages in parentheses)*

| *Course of DR* | *ECCE (8 eyes)* | *ECCE with IOL (10 eyes)* | *ICCE (16 eyes)* | *Total (34 eyes)* |
|---|---|---|---|---|
| From NoDR to NPDR | 2 (25) | 3 (30) | 3 (18 75) | 8 (23·5) |
| Aggravation of NPDR | 5 (62 5) | 6 (60) | 10 (62·5) | 21 (61·8) |
| Subtotal NPDR: | | | | 29 (85·3) |
| From NoDR to PDR | | | 1 (6·25) | 1 (2·9) |
| From NPDR to PDR | 1 (12·5) | 1 (10) | 2 (12 5) | 4 (11·8) |
| Subtotal PDR: | | | | 5 (14 7) |

ECCE=extracapsular cataract extraction. IOL=intraocular lens implantation. ICCE=intracapsular cataract extraction. DR=diabetic retinopathy. NoDR=no diabetic retinopathy. NPDR=non-proliferative diabetic retinopathy. PDR=proliferative diabetic retinopathy.

*Table 3 Progression of diabetic retinopathy during the first year after cataract extraction in relation to surgical technique (numbers of eyes with percentages in parentheses)*

| *Follow-up period* | *ECCE (8 eyes)* | *ECCE with IOL (10 eyes)* | *ICCE (16 eyes)* | *Total (34 eyes)* |
|---|---|---|---|---|
| F1 | 5 (62·5) | 6 (60) | 7 (43 75) | 18 (52·9) |
| F2 | 2 (25) | 3 (30) | 8 (50) | 13 (38·2) |
| F3 | 1 (12 5) | 1 (10) | 1 (6·25) | 3 (8·9) |

F1=between 2 weeks and 3 months after surgery. F2=between 4 and 6 months after surgery F3=between 7 and 12 months after surgery

## Results

Of the 89 patients 36 were men and 53 were women. The mean age at the time of surgery was 67·1 years (range 49 to 82 years) and the mean duration of diabetes mellitus was 10·1 years (range 6 months to 30 years). Cataract extraction was unilateral in 68 patients and bilateral in 21. In the bilateral cases only one eye, the one operated on first, was included in the study. Extracapsular cataract extraction was performed in 12 eyes (13·5%), ECCE with IOL in 37 (41·5%), and ICCE in 40 (45%).

During the first postoperative year 55 of the operated eyes (61·8%) showed 'no change' in retinal status and 34 (38·2%) showed 'progression' of diabetic retinopathy. The corresponding findings in the control group were 87·2% and 12·8% (Table 1).

Table 1 compares the clinical features of study patients and controls according to the findings ('no change' or 'progression') during the follow-up year. Among the operated patients there was no difference between the two subgroups with regard to sex distribution, mean age, mean duration of diabetes mellitus, or the presence of systemic disease. The only significant difference was related to the management of diabetes. Among the operated patients the diabetes was controlled by diet alone more often in patients who showed no change in their retinal status than patients who showed progression of retinopathy, whereas a greater number of patients whose retinopathy progressed needed hypoglycaemic agents and/or insulin for management of diabetes ($p<0·025$). A comparison between the clinical features of the study and control groups revealed no significant differences between them (Table 1).

The nature of the postoperative progression of diabetic retinopathy and its relationship to the surgical technique are summarised in Table 2. Of the 34 eyes that showed progression nine (26·4%) had no retinopathy prior to surgery but developed it afterwards and the rest (73·6%) showed progression of pre-existing retinopathy. The progression in most cases (29 eyes or 85·3%) took the form of aggravation of non-proliferative changes. However, five eyes (14·7%) developed PDR. Each of these patterns of postoperative progression of the retinopathy was observed for all three surgical techniques. As can be seen from Table 3, in 91% of these eyes the changes were

*Table 4 Visual acuity results after cataract surgery in relation to diabetic retinopathy (numbers of eyes with percentages in parentheses)*

| | *No change* (n=55 eyes)* | | | *Progression† (n=34 eyes)* | | |
|---|---|---|---|---|---|---|
| *Visual acuity‡* | *NoDR (n=38)* | *DR (n=17)* | *Total (n=55)* | *NoDR (n=9)* | *DR (n=25)* | *Total (n=34)* |
| ≥6/12 | 33 (87) | 12 (70) | 45 (82) | 6 (67) | 7 (28) | 13 (38) |
| 6/15–6/30 | 4 (10) | 3 (18) | 7 (13) | 2 (22) | 8 (32) | 10 (29) |
| <6/30 | 1 (3) | 2 (12) | 3 (5) | 1 (11) | 10 (40) | 11 (32) |

*Without postoperative deterioration of diabetic retinopathy
†With postoperative onset of retinopathy, or its deterioration either to more severe non-proliferative or to proliferative diabetic retinopathy. ‡Visual acuity at final follow-up visit.

*Table 5 Postoperative course of diabetic retinopathy in relation to its preoperative status*

| *Preoperative status* | *No. of eyes* | *No change (n=55 eyes) No. (%)* | *Progression (n=34 eyes) No (%)* | *p* |
|---|---|---|---|---|
| NoDR | 46 | 39 (71) | 7 (20) | <0 005 |
| DR | 43 | 16 (29) | 27 (80) | <0·005 |

*Table 6 Rate of progression of diabetic retinopathy during one year of follow-up after cataract surgery and in controls (present study) and in the general diabetic population (Nielsen's study[12 13])*

| | *Present study* | | | | *Nielsen Nonoperated* | |
|---|---|---|---|---|---|---|
| | *Operated** | | *Non-operated†* | | *Non-insulin use* | *Insulin use* |
| | *%* | *(No.)* | *%* | *(No )* | *%* | *%* |
| NoDR→NPDR | 9·0 | (8/89) | 4·3 | (3/70) | 3·7 | 3·7 |
| NPDR→NPDR‡ | 23·6 | (21/89) | 7·1 | (5/70) | 6·6 | 10·7 |
| NoDR→PDP§ | | | | | | |
| NPDR→PDR | 5·6 | (5/89) | 1·4 | (1/70) | 1·1 | 2·3 |
| Total | 38·2 | (34/89) | 12·8 | (9/70) | 11·4 | 16·7 |

*Operated eyes and †non-operated eyes. ‡Aggravation of NPDR
§As for Table 2.

*Table 7 Relationship between the preoperative status of diabetic retinopathy and its postoperative course for the different surgical techniques (numbers of eyes with percentages in parentheses)*

| | *ECCE with IOL (37 eyes)* | | *ICCE (40 eyes)* | |
|---|---|---|---|---|
| *Preoperative DR* | *No change (n=27)* | *Progress (n=10)* | *No change (n=24)* | *Progress (n=16)* |
| NoDR (42) | 24 (88·8) | 3 (30) | 13 (54 2) | 2 (12·5) |
| DR (35) | 3 (11·2) | 7 (70) | 11 (45·8) | 14 (87·5) |
| p | <0·005 | | <0·01 | |

already evident within six months of surgery. Moreover, in most of the eyes that underwent ECCE, with or without IOL, the change could already be detected within the first follow-up period – that is, within three months of surgery. By contrast, following ICCE the number of eyes showing the beginning of progression was similar in the first and the second periods of follow-up.

The final visual acuity results are summarised in Table 4. In eyes with no pre-existing retinopathy and no change in postoperative retinal status a visual acuity of at least 6/12 was achieved in 87% of the cases. By contrast, a relatively high proportion (40%) of eyes with pre-existing diabetic retinopathy and postoperative retinal deterioration had poor visual results of 6/30 or less.

The relationships between the preoperative retinal status and the postoperative course of diabetic retinopathy in the operated eyes are presented in Table 5. Eyes with NoDR preoperatively showed a significantly higher incidence of no change than of progression in their postoperative retinal status. In eyes with preoperative NPDR the opposite was true: their postoperative retinal status showed a significantly higher incidence of progression than no change ($p<0·005$). Table 6 compares the incidence of the various patterns of progression observed one year after cataract surgery in the study group with their corresponding incidence in the control group as well as in other nonoperated groups drawn from the general diabetic population.[12 13]

Since the results presented in Table 5 appear to indicate that the pre-existence of diabetic retinopathy could be considered a risk factor for its postoperative progression, we examined the relationship between the preoperative status of diabetic retinopathy and its postoperative course for each type of surgical technique (Table 7). In analysing this relationship we restricted the comparison to two surgical subgroups, ECCE with IOL and ICCE, since the number of cases in these two subgroups was similar and therefore comparable, while the number in the ECCE without IOL subgroup was small. The results show that, for both techniques, eyes without pre-existing diabetic retinopathy tended to remain stable more often than to deteriorate, while eyes with pre-existing NPDR tended to progress more often than to remain unchanged.

## Discussion

The aims of this study were (1) to find out if the eyes of diabetic patients who undergo cataract surgery are more prone than non-operated eyes of diabetic patients to develop or to show progression of diabetic retinopathy; (2) to identify the risk factors for postoperative progression of diabetic retinopathy; and (3) to follow the course of the disease in this particular group of operated patients. To achieve the last objective we attempted to eliminate any factors that might affect the natural course of the disease postoperatively. Accordingly, we excluded from the study group eyes with any additional diseases such as glaucoma or macular diseases other than diabetes, eyes that experienced operative complications such as vitreous loss or disruption of the posterior lens capsule, or eyes treated by laser photocoagulation before or immediately after surgery for pre-existing PDR or severe NPDR. Thus at the time of surgery the eyes in our study group presented only with NoDR or mild to moderate NPDR.

The differentiation between aphakic or pseudophakic cystoid macular oedema and diabetic cystoid macular oedema is a major problem.[3] In this series 'progression' of diabetic retinopathy was defined only where worsening of the characteristics typical for diabetic retinopathy were observed, regardless of whether foveal cystoid oedema was present or not. Thus patients with cystoid macular oedema, but with no evidence of other characteristics of diabetic retinopathy, were included in the 'no change' group.

Within 12 months of surgery diabetic retinopathy progressed in 38·2% of eyes that underwent cataract extraction as compared with only 12·8% in non-operated eyes over the same period (Table 6). The incidence of progression of diabetic retinopathy in our *control* group is in line with that reported by Nielsen,[12 13] who studied the course of diabetic retinopathy over a one-year period in the general diabetic population aged 30 or older at the time of disease onset (Table 6). On the other hand in a four-year study of the incidence and progression of diabetic retinopathy in patients aged at least 30 at the time of disease diagnosis Klein and associates found that worsening of retinopathy occurred in 34% of those who used insulin and in 25% of those who did not, while for development of PDR the corresponding rates were 7% and 2%.[14] The relatively high rates of progression of pre-existing NPDR and development of PDR found during the first postoperative year in our *study* group may be comparable to those reported by Klein *et al* in their four-year study. One could interpret these findings to suggest that the effect of cataract surgery on the progression of pre-existing NPDR and development of PDR might be equivalent to the natural course of the disease over four years in non-operated eyes. Since the pre-eminent risk variable for the occurrence of any diabetic retinopathy is thought to be the duration of the disease,[15-17] this interpretation, even though only speculative, should be kept in mind when planning cataract surgery for diabetic patients.

Klein *et al* also found a high rate of new onset of retinopathy in patients who had been free of retinopathy at the start of the four-year study.[14] In contrast, the commonest pattern of progression seen in our study group was worsening of pre-existing NPDR (Table 2). In addition we found that retinal deterioration occurred nearly four times (7/27) as often in eyes with pre-existing diabetic retinopathy as without it (Table 5), thus pointing to the pre-existence of diabetic retinopathy as a possible risk factor for its postoperative progression.

The more frequent deterioration of diabetic retinopathy in our study group than in non-operated eyes of this and of other series[2 4 5] appears to support earlier suggestions that removal of the lens may result in a progression of diabetic retinopathy and/or development of rubeosis iridis,[18 19] in contrast to the findings reported by Sebestyen,[7] who observed similar progression of retinopathy in operated and non-operated eyes. It is not yet clear how the removal of the lens may affect diabetic retinal changes in general. However, with regard to one specific characteristic of diabetic retinopathy – the occurrence of endothelial proliferation and neovascularisation – Williams *et al*[20] showed that human lens extracts can inhibit endothelial proliferation. Therefore their removal may induce vascular alterations resulting in neovascularisation. Furthermore they also demonstrated considerable inhibition of endothelial cell activity in extracts of bovine lens capsule,[20] and suggested that the presence of an intact lens capsule may inhibit the development of iris neovascularisation. Clinical experience seems to support these findings.

Aiello *et al*[18] found that, following ICCE, patients with or without background retinopathy were at particularly high risk of developing vitreous haemorrhage, presumably reflecting progression of the disease to PDR. Alpar[5 6] observed deterioration of diabetic retinopathy in some diabetic patients following either ICCE or ECCE, with the least progression occurring in patients who underwent ECCE with IOL implantation in the capsular bag. In the present study we also found progression of diabetic retinopathy following both procedures, with a lower incidence in cases of ECCE with IOL (10 out of 27 eyes, 37%) than in ICCE (16 out of 40 eyes, 40%) (Table 7). However, this finding could be explained at least partially by the lower proportion of eyes at risk because of pre-existing NPDR in the group undergoing ECCE with IOL (27%, 10 out of 37 eyes) than in the ICCE group (62·5%, 25 out of 40 eyes) (Table 7). Although clinical evidence suggests that ICCE may have a more deleterious effect than ECCE on the postoperative course of diabetic retinopathy, the precise role of the posterior lens capsule in reducing vascular complications after cataract surgery in diabetic patients requires further investigation.

Of the 34 eyes in our study that showed postoperative retinal deterioration the majority (85·3%) did not progress to PDR but remained at the non-proliferative stage, sometimes with postoperative macular oedema, which affected the final visual results. The visual outcome following cataract surgery in our study (Table 4) was especially poor in patients with pre-existing diabetic retinopathy who showed postoperative progression; it should however be noted that in the progression subgroup, good visual acuity was achieved in 67% of eyes with preoperative NoDR and in 28% of eyes with preoperative NPDR. The largest subgroup (87%) to achieve good visual results consisted of patients with no pre-existing diabetic retinopathy and no change postoperatively.

The only significant difference in general clinical conditions between patients with no change in retinal status and patients with postoperative progression of diabetic retinopathy related to the management of diabetes: more patients in the 'no change' group than in the 'progression' group were managed by dietary control alone (Table 1).

The results of this study clearly indicate that progression of diabetic retinopathy is not uncommon after cataract surgery, even when the technique employed is ECCE. Patients with diabetic retinopathy prior to surgery are at higher risk for progression. Accordingly these patients should be closely monitored postoperatively for early signs of progression of diabetic retinopathy and where necessary should be considered candidates for laser treatment. Diabetic patients scheduled for cataract extraction should be informed that surgery may have an adverse influence on diabetic retinopathy and that this may affect the final visual outcome. The preoperative status of diabetic retinopathy may be a significant prognostic factor for the postoperative outcome.

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# Alterations in elastin of the optic nerve head in human and experimental glaucoma

Harry A Quigley, Andrew Brown, Mary Ellen Dorman-Pease

## Abstract

**The optic nerve heads from normal and glaucomatous eyes of humans and monkeys were examined by light and electron microscopy for the presence and distribution of elastin. Elastin densely lined the insertion of the lamina cribrosa into the sclera and was prominent in the laminar beams. The long axis of elastin paralleled that of the collagen fibrils and corresponded to the directions of expected forces on the tissue. In glaucomatous eyes elastin molecules were curled instead of straight and seemed disconnected from the other elements of the connective tissue matrix. Laminar beams stretch and reorganise their substructure during glaucomatous atrophy, probably leading to changed compliance. Differences in elastin function may have a part in susceptibility to glaucomatous injury.**

Glaucoma is best defined as an optic neuropathy associated with a characteristic excavation of the optic disc[1] and a progressive loss of visual field sensitivity. This neuropathy is related to the level of the intraocular pressure (IOP) such that, the higher the IOP the more likely the neuropathy is to occur.[2] In some persons it develops at what is considered normal IOP, while in many others the IOP is intermittently or consistently above the statistically normal level.

The IOP acts on the optic nerve head and the sclera by two force vectors. Firstly, the IOP is usually higher than optic nerve tissue pressure, generating an inside-out force. Secondly, the IOP generates a wall tension that pulls on the perimeter of the nerve head. The tissues at this complex opening in the eye wall are specialised to account for these forces.[3-5] This specialised composition allows the safe passage of nerve fibres out of the eye and the maintenance of an appropriate blood supply to them under normal conditions.

We have conducted detailed studies of the extracellular connective tissues of the optic nerve head. Collagen, glycosaminoglycans, and elastin are instrumental in determining the response of the eye to the forces produced by IOP. Anderson[6] may have been the first to describe the presence of elastin within the lamina cribrosa by electron microscopy. We here demonstrate the detailed distribution of elastin in the normal optic nerve head by electron microscopy and by a histochemical method not previously used in ocular tissues. These techniques illustrate how elastin may contribute to the biomechanical response of the nerve head. Features of extracellular structure may have an important role in determining the susceptibility of the individual eye to pressure-induced forces. In addition we present the eyes of human eye bank donors wh had had glaucoma and the eyes of monkeys wit experimental glaucoma. The appearance of elastin fibres and the surrounding connective tissu elements are dramatically changed by the IOP.

## Material and methods

We studied 10 human eyes that had no history o eye disease and 19 human glaucomatous eye with a history of raised IOP and/or clinica glaucomatous damage. Only one eye per perso was examined. Control eyes had a normal neura area in their optic nerve cross-section, which wa embedded in epoxy resin, thick-sectioned a 1 μm, and analysed.[7 8] Normal and glaucomatous donors did not differ in age (mean=74 year in each group, p>0·05); 90% of both dono groups were Caucasian, and the two groups wer equally divided between men and women.

Human glaucomatous eyes were fixed in buffered aldehydes within 24 hours of death. Th degree of glaucomatous damage was determine by the visual field test result, the optic nerv neural area and/or fibre count, or both (Table 1) Nineteen glaucomatous eyes were studied b light microscopy, at least three from each of th five severity stages. In addition we examined b electron microscopy six normal and seve glaucomatous human eyes, two each from stage 1, 4, and 5 and one from stage 3.

In cynomolgus monkeys (*Macaca fascicularis* we caused a raised IOP in one eye by lase trabecular treatment.[9] This produces an opti neuropathy that is indistinguishable fro human glaucoma in clinical and histopathological details. The animals were anaesthetise with intravenous pentobarbitone, killed b exsanguination, the eyes fixed by vascular perfusion of aldehyde fixatives, and the optic nerv heads of their damaged and normal eyes dissected as described below. We studied the nerv heads of five glaucomatous monkey eyes an their fellow eye controls. The degree of injury i monkey eyes was judged by the degree of fibr loss in the optic nerve cross sections in simila fashion to human eyes. Two of the monkey eye had stage 3 damage and three had stage

*Table 1 Criteria for severity staging of human glaucoma ey*

| | Visual field | Optic nerve area |
|---|---|---|
| Stage 1* | Normal | >85% of normal |
| Stage 2 | Normal | 75–85% of norma |
| Stage 3 | Usually abnormal | 50–75% of norma |
| Stage 4 | Abnormal | 25–50% of norma |
| Stage 5 | Advanced loss | <25% of normal |

In seven of the 19 eyes only one of the two parameters was available.
*Stage 1 consists of eyes suspected of being glaucomatous that ha statistically abnormal intraocular pressure.

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damage. This research complied with the ARVO Resolution on Animals and was approved and monitored by the Johns Hopkins Animal Care Committee.

For light microscopy we removed the optic nerve head and trimmed the surrounding sclera to identify the superior position. The tissue was rinsed in phosphate buffer, and the retina was removed. Nerve heads were placed in 30% sucrose in distilled water for cryoprotection, frozen in liquid nitrogen, and serially sectioned at 10 μm thickness parallel to the interface of the nerve head with the vitreous cavity. This method gave similar tissue preservation to paraffin embedding. Frozen, unfixed sections were stained by Luna's method, whose major steps are: (1) 30 minutes in aldehyde fuchsin; (2) alcohol rinse; and (3) 1 minute in haematoxylin to stain the alpha elastin fibres.[10] By staining alternate sections we found the Luna technique to be superior to Verhoeff-van Gieson and other histochemical methods for highlighting the three-dimensional elastin network. We confirmed by electron microscopic methods described below that the position and relative number of stained elements with the Luna method correspond to alpha elastin. In addition our previous light microscopic studies of staining of alpha elastin by antibodies labelled by the immunoperoxidase method indicate that the distribution of stained material is similar to that obtained with the Luna method. The nerve heads were analysed by region in the normal eyes (superior, inferior, nasal, temporal). In the glaucomatous eyes the degree of nerve fibre loss within an optic nerve cross section[7,8] was correlated with the appearance of elastin in each region. The findings in human and monkey eyes were similar, but only human examples are presented here.

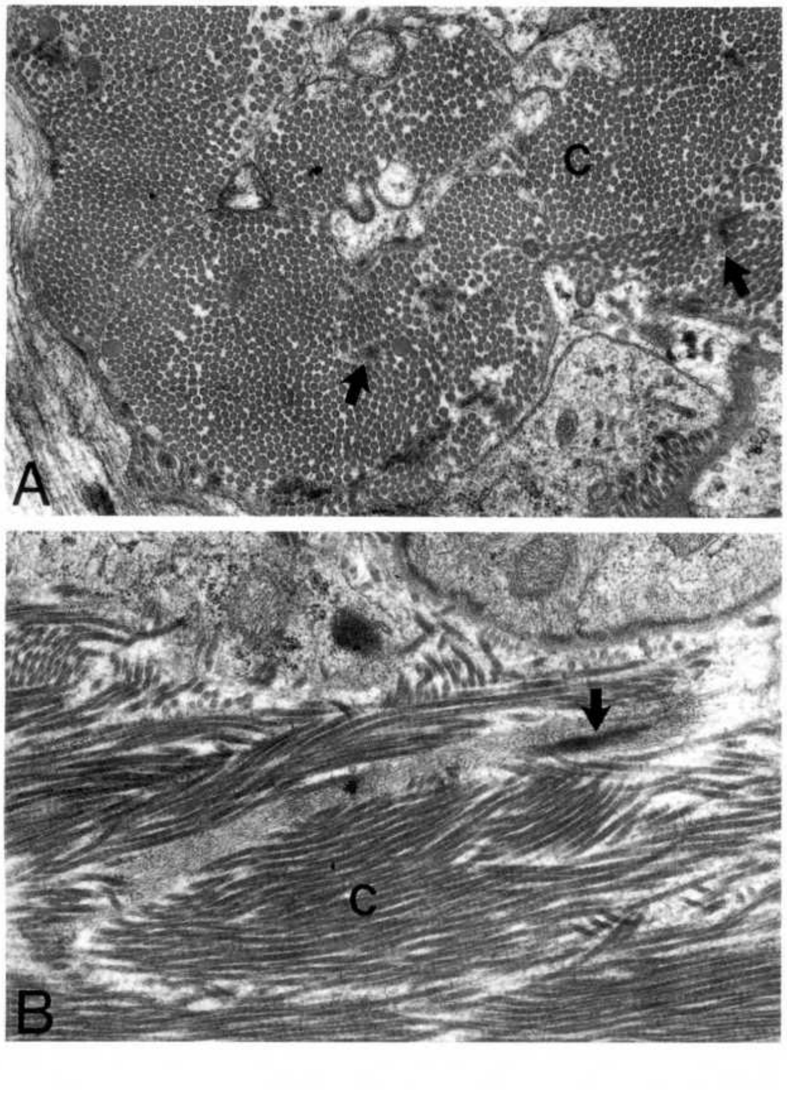

*Figure 1 Transmission electron micrographs of lamina cribrosa beam structure. A: Collagen fibrils (C) are seen in cross section and elastin complexes (arrows) are parallel to collagen, therefore also appearing in cross section. B: Collagen (C) and elastin (arrows) are both in longitudinal section. (Normal monkey nerve head, ×17 000.)*

For electron microscopy nerve heads were postfixed in 1% osmium tetroxide and stained with tannic acid, uranyl acetate, and lead citrate after thin sectioning, to define better the alpha elastin.[11] We have demonstrated previously that the elements referred to as elastin fibres[12] stain with antibodies to alpha elastin.[13]

## Results

Our normal material provided an important comparison with the glaucomatous tissues prepared by the same methods. There was a large amount of elastin in the optic nerve head region. The specificity of the Luna stain was confirmed by staining of Bruch's membrane and arteriolar walls. The peripapillary sclera had more elastin than the sclera distant from the nerve. By electron microscopy the long axes of elastin fibres were parallel to the orientation of the collagen bundles in which they resided (Fig 1). Elastin stained darkly with tannic acid, and the specificity of this staining had been previously confirmed by labelling with antibodies against alpha elastin conjugated with gold particles (Fig 2).

In the immediate 200–300 μm zone of insertion of the lamina cribrosa, elastin fibrils ringed the nerve head in a dense band (Fig 3). From this ring elastin fibrils originated at nearly a right angle, entering the base of each beam of the lamina cribrosa. Each laminar beam had several elastin fibres, with collagen spaced between them (Fig 4). The elastin fibres in the normal human or monkey lamina were invariably straight in appearance, bending only slightly as they passed from one beam to another. There were only minimal differences between regions of the nerve head cross section in elastin distribution. However, anteroposteriorly elastin density was highest at the level of the sclera and lower at the level of the retina and posterior to the line of myelination (Fig 5).

In the stage 1 glaucomatous eyes no definite differences from the normal pattern of elastin staining were observed with light or electron microscopy. In all the stage 2 nerve heads the appearance of elastin was abnormal. In some beams the normally straight elastin molecules appeared curvilinear, like small sine waves (Fig 4). This was most prominent in atrophic zones of the nerve. At damage stages 3 and 4 every eye had curved elastin profiles in many beams. In eyes with severe damage (stage 5) the interpretation of the findings was made difficult by the extreme change in laminar architecture.

We correlated the sectors of substantial neural loss with the presence of curled elastin. Six eyes were not included in this analysis because their damage was uniform. Moreover, we excluded the four stage 5 eyes that had nearly total loss of fibres. In five of the remaining nine eyes the most

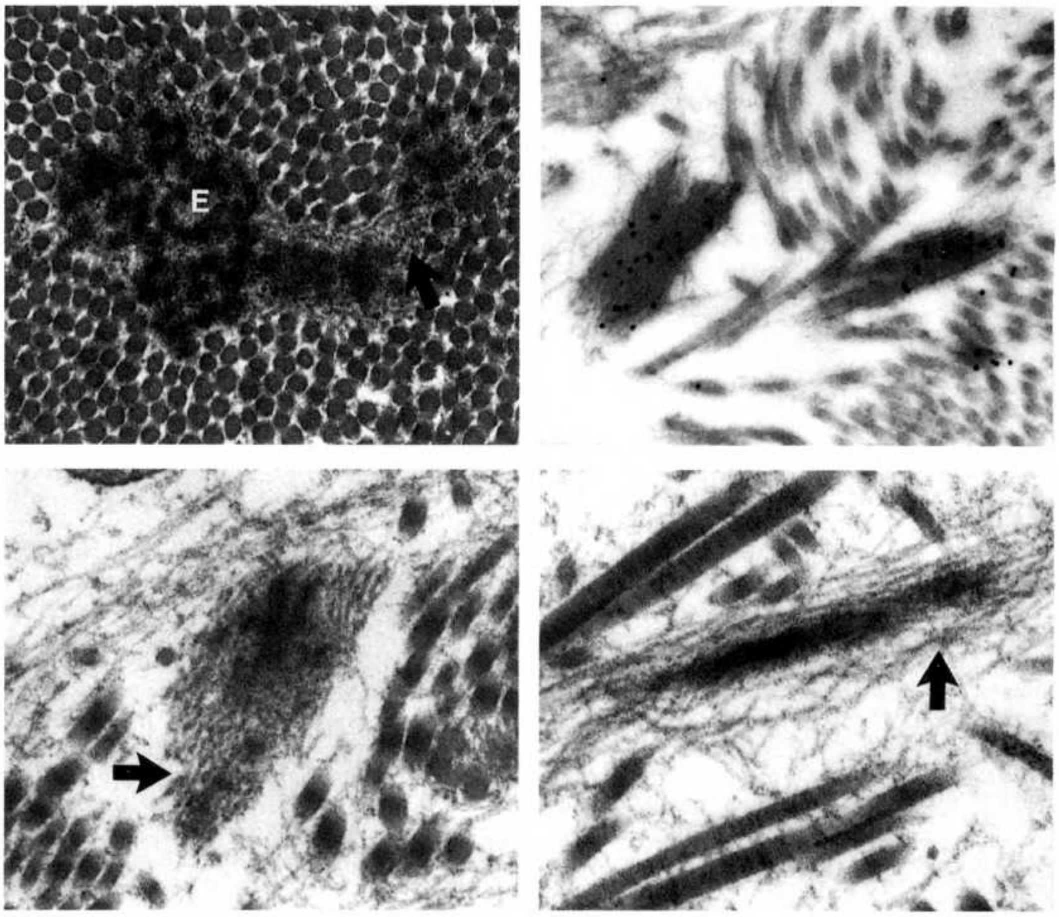

*Figure 2 Collagen and elastin from normal monkey lamina cribrosa (upper left) shows the normally close apposition of collagen fibrils to the microfibrillar component of the elastin complex (arrows). The upper right micrograph from a normal human lamina shows that the darkly stained core (white E in upper left) is labelled by antibodies against alpha elastin that were conjugated with 15 nm colloidal gold particles.[4] The two lower micrographs are from lamina of monkeys with experimental glaucoma. Note the much greater separation between elastin's microfibrils (arrows), compared with the normal appearance upper left. (The separation present in the gold-labelled specimen, upper right, is due to preparation conditions necessary for immunoelectron microscopy.) (Upper left, lower right and left: monkey, ×48 000; upper right, normal human, ×37 000).*

prominent change in elastin appearance was in the area(s) of nerve loss.

The number of elastin fibres in the glaucomatous eyes seemed qualitatively normal. It proved impossible to quantify elastin fibres by light microscopy. We are at present conducting quantifications by other techniques.

By electron microscopy the normal laminar beams were surrounded by astrocytes and their basement membrane. The beam core consisted of fibrillar collagen (types I, III, and VI), elastin, glycosaminoglycans, and the laminar capillaries with their associated basement membranes (Fig 1). Even in the mildly damaged glaucomatous eyes the lamina cribrosa beam structure was disrupted, leading to a lower density of those

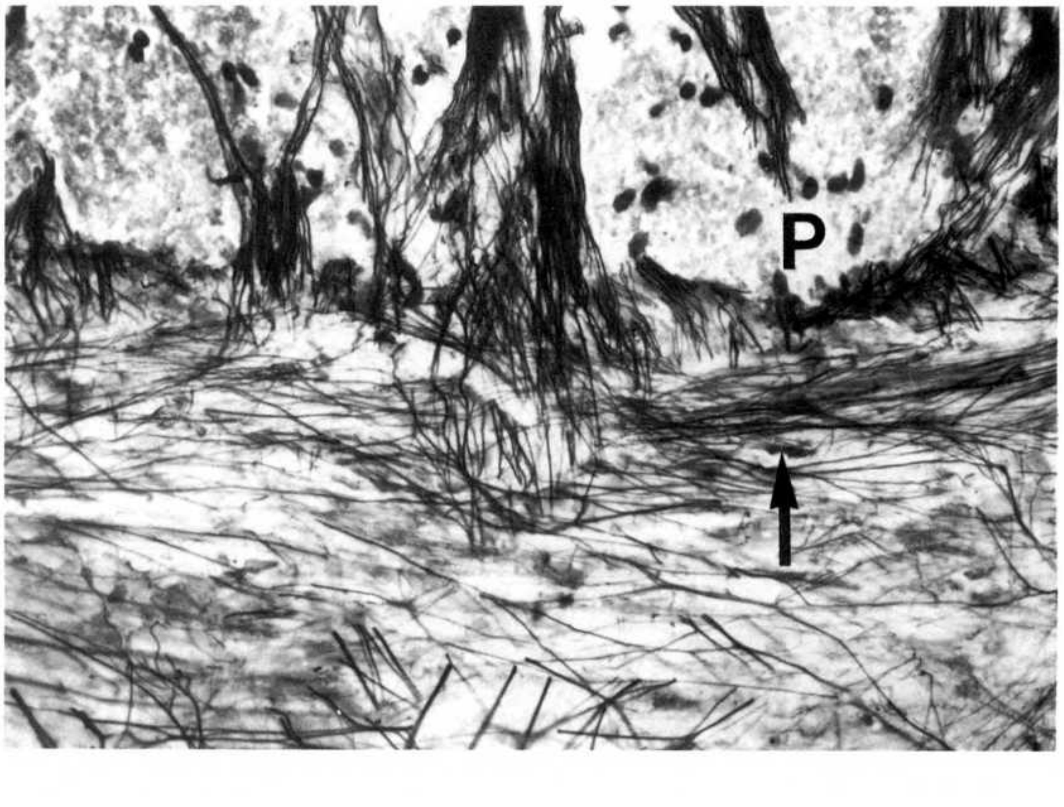

*Figure 3 Zone of sclera immediately adjoining the nerve head (insertion zone). Note dense ring of elastin surrounding nerve head opening (arrow) and elastin of most peripheral lamina cribrosa beam perpendicular to the ring passing from scleral rim into nerve head between neural pores (P). (Normal human eye, Luna method, frozen section, ×540.)*

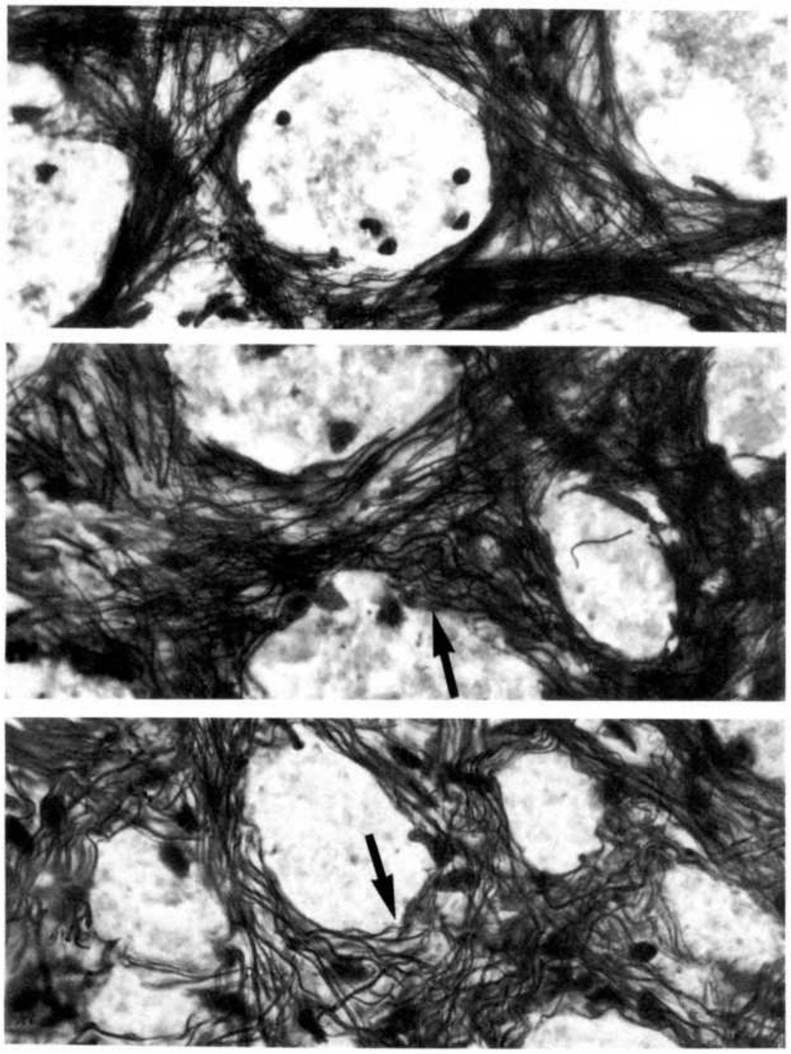

*Figure 4 Light micrographs showing lamina cribrosa beams stained for elastin in nerve heads classified as normal (upper), mildly damaged (middle), and severely damaged (lower). The normal elastin appearance (upper) consists of straight elastin fibres spaced evenly across the beams. In the mildly and severely damaged glaucomatous eyes the elastin fibres are curved (arrows) rather than straight. (Human normal and glaucoma stage 2 and stage 4; Luna method, frozen sections, ×490.)*

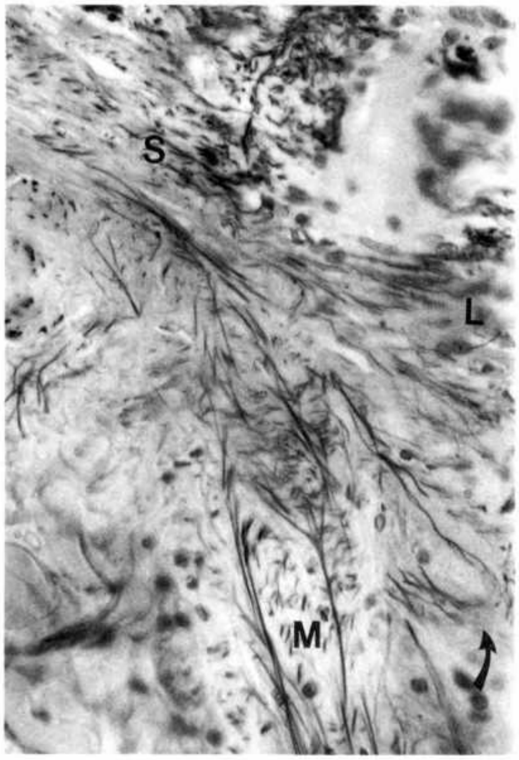

*Figure 5 Light micrograph of elastin at scleral insertion of nerve head (S). Elastin in laminar beams (L) runs straight across the nerve head opening (left to right), while that in the meninges (M) is parallel to the long axis of the optic nerve. The septa of the optic nerve behind the line of myelination contain elastin with various directional orientations (arrow). (Normal human eye; Luna method with epoxy resin embedding, ×350.)*

components visible by electron microscopy (Fig 6). The better preservation of the monkey eyes provided a clearer view of this change, but it was present in the human material as well. The beams underwent a movement toward the myelinated nerve from their original position. This was evident in our specimens as a loss in their astrocytic covering, and the development of electron lucent spaces between collagen and elastin fibrils (Fig 7). In the normal laminar beam collagen and elastin are tightly packed together. In the glaucomatous nerve heads, however, elastin fibres were less closely apposed to fibrillar or basement membrane collagen than in normal tissue (Figs 2, 6, 7). The ultrastructural substructure of the elastin fibres was not different in normal and glaucomatous eyes.

## Discussion

Hernandez and coworkers[14] found that the area of the sclera immediately adjacent to the lamina is rich in elastin and that there is a circumferential orientation to the molecules. They also found elastin within laminar beams, orientated preferentially across the nerve head opening. We confirm that the densest accumulation of elastin at the normal nerve head is at the insertion ring immediately surrounding the lamina, at the base of the most peripheral beams of the lamina. Here the long axis of elastin fibres is orientated circumferentially. Biomechanical analysis of a hole in a walled structure indicates that the stress at the edge of the hole might be several times that of the wall tension itself.[15] Both elastin and collagen are concentrated in amount and position at this location in a way that appears to resist forces that would tend to enlarge the nerve head opening.

The long axis of elastin fibres is typically parallel to that of the collagen fibrils in the lamina. Throughout the nerve head both fibrillar species run across the lamina from one edge of the nerve head to the other. Elastin fibres are usually straight in appearance in the normal lamina. It is logical that the maximum resistance to the deformation of laminar beams is in the plane across the nerve head, compared with forces exerted from inside outward. This may explain why the most prominent change in the structure of nerve head in glaucoma is not enlargement of its diameter at the level of Bruch's membrane,[16] but an anteroposterior compression of the laminar plates.[7]

Laboratory investigations show that the primary function of elastin is to resist tissue deformation and to return its shape to normal at low levels of stress.[17] Elastin consists of complexes of a 72 000 molecular weight polypeptide,[18] deposited on a microfibrillar matrix (fibrillin).[13] Elastin stretches under stress and returns to its original length after release of tension. Collagen appears to function in load bearing with moderate and severe stress.[19] It is capable of resistance to elongation but does not restore the original position or length of the tissue as effectively as elastin does.

In both human and monkey glaucoma we found that the elastin within the lamina cribrosa appeared wavy in outline rather than straight, as

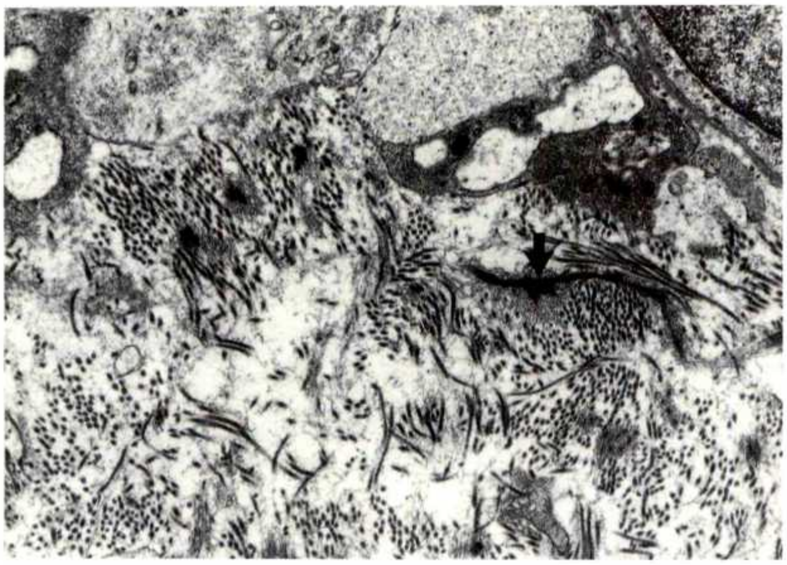

*Figure 6 Lamina cribrosa beam in a monkey eye with experimental glaucoma damage. Note that by comparison with similar area in a normal monkey eye (Figure 1A) there is a dramatic disorganisation of the beam. The normal tightly packed appearance is changed to one with substantial optically empty zones among collagen fibrils and elastin molecules (arrow). (Monkey; ×12 000.)*

in normal tissue. This is not likely to be an artefact of tissue preservation or handling. Both normal and glaucomatous eyes were fixed and sectioned identically, yet only glaucomatous eyes had wavy elastin. It was present in frozen-sectioned and plastic-embedded tissues, and with a variety of elastin stains (though most vividly with Luna staining). The wavy appearance was found in both human and experimental monkey glaucomatous eyes. Finally, it was more likely to be found within the same nerve head in areas of damage compared with areas that were less atrophic.

These facts leave little doubt that the wavy appearance is a characteristic change in the substructure of the glaucomatous lamina cribrosa. We do not know whether it is a causal factor in neural damage or a simple result of the rearrangement of nerve head tissues typical for glaucoma. The wavy elastin was detected as early as our stage 2, a group of eyes with either normal visual field tests or more than 75% of the normal number of optic nerve fibres. This places the finding relatively early in glaucoma damage.

Electron microscopically, the relationship of elastin fibres to visible collagen was also changed in glaucomatous eyes. In normal laminar beams, collagen fibrils or basement membranes are immediately next to the microfibrillar network of the elastin complex. After glaucoma injury elastin appeared to be separate from other elements in disorganised laminar beams. Since there were many beams with collagen fibrils orientated randomly rather than in typically organised fashion, it is reasonable to suppose that irreversible elongation of laminar beams occurred.[20,21] Normally elastin may be directly connected to collagens type I, III, IV, or VI.[13] If the collagen bundles lose their normal structure, the elastin network might be disconnected from the other elements of the connective tissue. This may explain the change in elastin appearance seen by light microscopy. One possibility is that the elastin is analogous to a spring that is normally stretched in a straight line between two fixed points. When disconnected from a fixed framework, the spring assumes a curled shape. Alternatively, the wavy appearance of the elastin might have resulted from other causes. For example, the internal structure of the fibres might have been altered. However, we could not detect ultrastructural differences between the elastin fibres in glaucomatous and normal eyes.

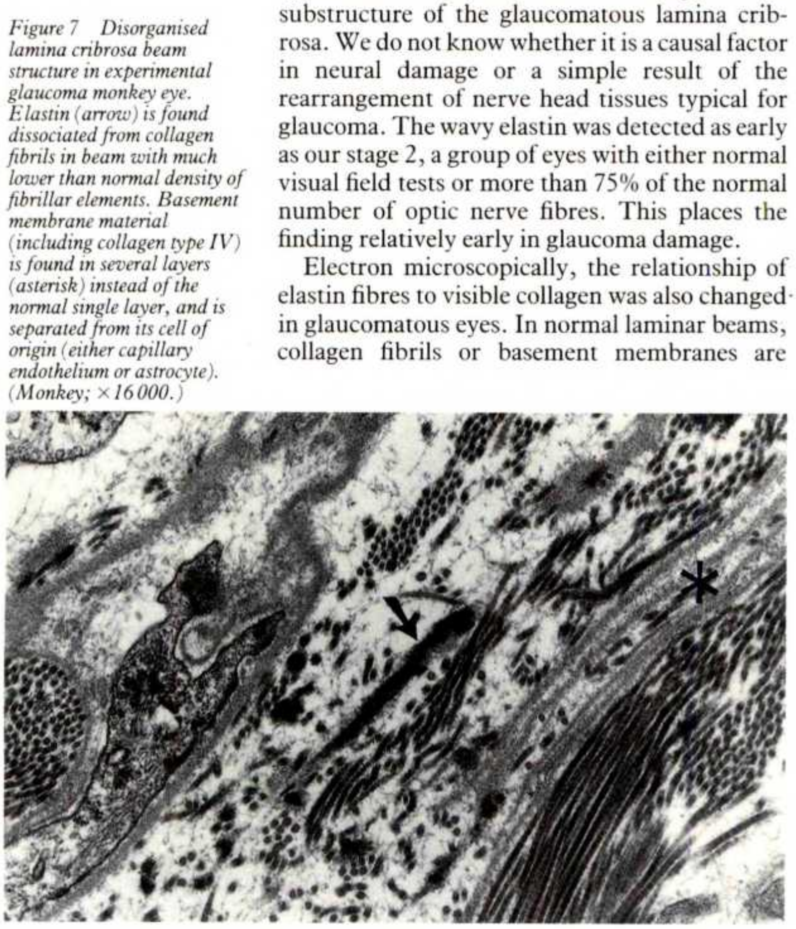

*Figure 7 Disorganised lamina cribrosa beam structure in experimental glaucoma monkey eye. Elastin (arrow) is found dissociated from collagen fibrils in beam with much lower than normal density of fibrillar elements. Basement membrane material (including collagen type IV) is found in several layers (asterisk) instead of the normal single layer, and is separated from its cell of origin (either capillary endothelium or astrocyte). (Monkey; ×16 000.)*

The curled appearance of collagen within the disorganised laminar beams is only one of a number of changes in laminar connective tissue in experimental or human glaucoma. There is strong evidence that changes occur in laminar collagen. Biochemical analyses suggest a difference in the amino acid composition of collagen in normal as compared with glaucomatous eyes.[22] Changes in the amount or distribution of collagen were also suggested by immunohistochemical labelling of collagens.[20,21] In a previous immunoelectron microscopic study[21] we demonstrated reduplicated basement membrane, consisting in part of collagen type IV, within the former neural bundle areas of experimental glaucoma nerve heads. This is in a different position and has a different appearance from the curled elastin within affected laminar beams reported here.

The alterations in elastin and collagen in glaucoma may change the biomechanical behaviour of the lamina. In this regard our observations appear to be consistent with measurements of optic nerve head compliance made by Zeimer and Ogura that indicate an increased stiffness with advanced glaucomatous damage.[23]

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# Association of Vistech contrast sensitivity and visual field findings in glaucoma

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## Abstract

**Single eye visual fields and contrast sensitivity were assessed in 60 subjects, who were being followed up in a glaucoma clinic for manifest glaucoma or a suspicion of glaucoma because of raised intraocular pressure. The Fieldmaster 5000 (static/kinetic perimeter) was used for the visual fields, and a Vistech wall chart sine wave grating test was used for contrast sensitivity measurements. The subjects were divided into three groups – defect (D), suspect (S) and normal (N) – on the basis of their perimetric findings by subjective grading of 16 perimetric scoring categories for each visual field. The mean Vistech sensitivity levels were not found to be significantly different between the D, S, and N field subgroups at any of the five spatial frequencies provided on the test charts (1·5, 3, 6, 12, and 18 cycles per degree). Complex algorithms combining results from two or more spatial frequencies also failed to yield any significant differences between the groups. Diagnostic sensitivity and specificities relating Vistech contrast sensitivity findings to groups N and D never concomitantly exceeded 60%.**

Measurement of the visual fields is the principal method for confirming the presence and progression of glaucoma. Despite recent advances in computerised visual field analysis, perimetric studies remain time consuming and demand complex subjective interpretation. Psychophysical research has revealed abnormalities in contrast sensitivity in association with glaucoma and ocular hypertension.[1-6] Recently clinical methods for presenting static contrast gratings on wall charts have been introduced.[7 8] One of these is the Vistech sine wave grating method. Bron has reported that oscilloscopic and Vistech methods discriminate glaucomatous from ocular hypertensive eyes equally well.[9] The purpose of the present study was to assess the association between visual fields, categorised by traditional criteria, and concomitant Vistech contrast sensitivity measurements.

*Table 1 Criteria used for interpretation of visual fields*

| | |
|---|---|
| 1 Normal, peripheral | No defect seen |
| 2 Borderline peripheral | |
| (*a*) Nasal hemianopic offset | 10° or greater offset nasal to vertical midline |
| (*b*) Peripheral constriction, temporally or vertically | Isopter inside 50° temporally 40° inferiorly, or 30° superiorly |
| 3 Defect, peripheral | |
| (*a*) Nasal step | 10° or greater offset above or below the horizontal raphe, nasally |
| (*b*) Peripheral constriction, nasally | Isopter inside 30°, nasally |
| (*c*) Temporal sector defect | 20° or greater defect toward blind spot in temporal isoptre |
| (*d*) Temporal hemianopic offset | 10° or greater offset temporal to vertical midline |
| 4 Normal, central | zero or one defect* point |
| 5 Borderline, central | |
| (*a*) Paracentral depression | 2 to 5 non-contiguous defects in Bjerrum area |
| (*b*) Enlarged blind spot | 2 to 5 contiguous defects next to blind spot (not all in Bjerrum area) |
| (*c*) Peripheral depression | 3 or more contiguous defects outside Bjerrum area |
| (*d*) Diffuse depression | All points equally depressed |
| 6 Defect, central | |
| (*a*) Paracentral scotoma | 2 to 5 contiguous defects in Bjerrum area |
| (*b*) Seidel scotoma | 2 to 5 contiguous defects next to blind spot in Bjerrum area |
| (*c*) Arcuate scotoma | 6 or more contiguous defects in Bjerrum area (single or double) |
| (*d*) Nasal step | 2 or more defects above or below horizontal raphe in nasal periphery |
| (*e*) Temporal sector defect | 6 or more contiguous defects temporal to blind spot |

*Defect refers to depression of 6 dB or more below age-related retinal threshold for point being tested.

*Table 2 Comparison of Vistech line scores A through E* (1·5, 3, 6, 12, and 18 cycles per degree) for normal, suspect and defect groups*

| | *Normal* | *Suspect* | *Defect* |
|---|---|---|---|
| Number | 16 | 13 | 31 |
| Line score A | 5·1 (0·2) | 5·0 (0·2) | 5·0 (1·0) |
| Line score B | 5·5 (0·3) | 5·7 (0·2) | 5·4 (0·1) |
| Line score C | 4·5 (0·4) | 4·8 (0·3) | 4·3 (0·3) |
| Line score D | 3·3 (0·6) | 3·8 (0·5) | 3·5 (0·3) |
| Line score E | 2·8 (0·5) | 2·8 (0·5) | 2·4 (0·3) |

*Standard errors are in parentheses. No significant differences between the three groups were found.

## Materials and methods

The study population consisted of subjects who were being followed up in the Glaucoma Clinic of Duke University Eye Center for manifest glaucoma or a suspicion of glaucoma on the basis of intraocular pressure elevation. Visual fields were assessed with the Fieldmaster 5000 (static/kinetic perimeter; Bausch and Lomb, Rochester, NY), and contrast sensitivity was measured under conditions of constant illumination with Vistech sine wave gratings (Vistech Consultants, Dayton, Ohio). The Fieldmaster 5000, the details of which have been previously described,[10] is a fully automated perimeter which measures the peripheral field with a kinetic target and the central 30° with static targets. In the present

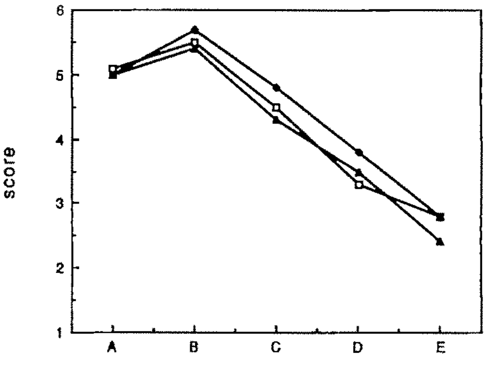

*Figure 1 Average Vistech contrast sensitivity line scores for normal, suspect, and defect groups. Lines A–E correspond to five static spacial frequencies: 1·5, 3, 6, 12, and 18 cycles per degree. Normal □. Suspect ◆. Defect ▲.*

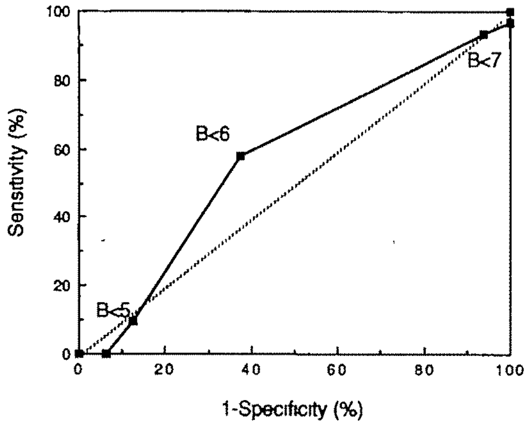

*Figure 2 Receiver operator characteristic (ROC) curve showing Vistech line B score (3 cycles per degree) as a detector of glaucomatous field loss. Criteria for abnormal classification are indicated along the curve.*

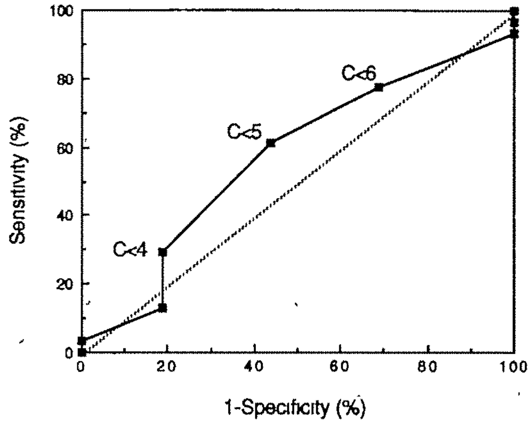

*Figure 3 ROC curve showing Vistech line C score (6 cycles per degree) as a detector of glaucomatous field loss. Criteria for abnormal classification are indicated along the curve.*

study the central, static points were first tested with a supratheshold stimulus, followed by full thresholding of all points missed on the initial presentation, and the peripheral field was measured with a single isopter. The Vistech wall chart system provides a rapid score on an integral scale from 0 to 8, corresponding to the number of patterns correctly identified, for each of five static spatial frequencies. These frequencies, 1·5, 3, 6, 12, and 18 cycles per degree, are defined as lines A through E respectively.

Visual fields were evaluated in masked fashion by glaucoma clinicians (MBS and WCS) into defect (D), suspect (S), and normal (N) categories on the basis of detailed subjective criteria which involved pass/fail grading into a total of 16 separate subcategories (Table 1). Patients assigned to group D included those with definitive glaucomatous changes or >2 borderline abnormalities. Group N included those subjects with no abnormal findings, and group S included the remainder. When both fields from a single subject fell into the same rating group, one was randomly selected for analysis. Otherwise the eye with the greater defect was included, so that only one eye from each subject was considered. All eyes under study had visual acuities of 20/40 or better. Differences between the two groups were analysed by the unpaired *t* test. Sensitivites and specificities were determined for a variety of criteria, with Vistech scores being used as detectors of glaucomatous field loss.

## Results

Sixty patients were included in the study, 31 in group D, 13 in group S, and 16 in group N. The mean ages for the D, S, and N subgroups were: 54 (range 25–76), 55 (range 29–78), and 53 (range 25–72) respectively. Table 2 and Fig 1 show the average contrast sensitivity scores for the three groups. Mean scores of the D, S, and N field groups did not differ significantly at any of the five spatial frequencies provided on the test charts. Complex algorithms looking for midrange deficit – that is, average (A, B) –C; A–average (B, C); A+D–B; A+D–C; A+B–(C+D); A+D–(B+C); B–C; A–C; A–B) – also failed to yield any significant mean differences between the groups. Diagnostic sensitivity/specificity (receiver operator characteristic; ROC) curves relating Vistech contrast sensitivity findings to perimetry groups N and D are shown in Figs 2 and 3 for lines B and C (3 and 6 cycles per degree). These data suggest that Vistech contrast sensitivity scores of B<6 or C<5 offer the greatest combination of diagnostic sensitivity and specificity. A looser cutoff point (B<7 or C<6) would include many normal subjects, while a more rigid cutoff limit (B<5 or C<4) would miss many glaucomas. Vistech results at or below the latter levels, however, would provide a reasonable indication of pathology, with false positive rates of <20%. Table 3 includes sensitivity/specificity values for classification criteria involving lines B and C. Three criteria produce sensitivity and specificity values concomitantly greater than 50%: B<6, C<5, and average (B, C) <5. None produced sensitivity and specificity values concomitantly exceeding 60%.

*Table 3 Sensitivity and specificity values using Vistech line scores B (3 cycles per degree) and C (6 cycles per degree) as detectors of glaucomatous field loss*

| *Abnormal classification* | *Sensitivity* | *Specificity* |
|---|---|---|
| B<6 | 58·1% | 62·5% |
| C<5 | 61·3% | 56·3% |
| C<5 and B<6 | 48·4% | 68·8% |
| C<5 or B<6 | 71·0% | 50·0% |
| average (B and C) <5 | 68·8% | 51·6% |

## Discussion

The sensitivity/specificity values obtained in the present study for contrast sensitivity scores are low, with the best association with subjectively classified visual fields seen at 3 and 6 cycles per

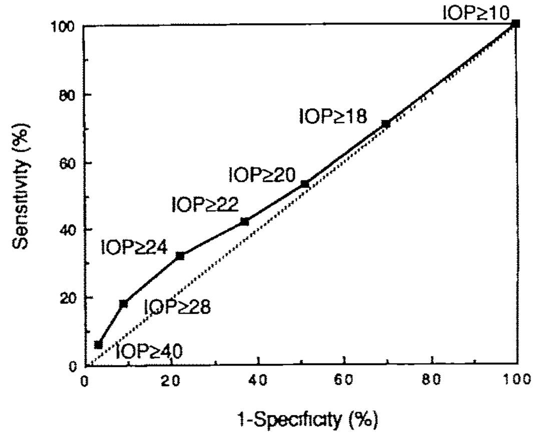

*Figure 4 ROC curve showing intraocular pressure (IOP in mmHg) as a detector of glaucomatous field loss. Criteria for abnormal classification are indicated along the curve Adapted from Hill[11] based on data from Daubs and Crick.[12]*

degree. These sensitivity/specificity curves are nevertheless more definitive than published associations between intraocular pressure and visual fields (Figure 4).[11 12] The findings presented here are consistent with those of Adams *et al*[13] who found that mean contrast sensitivities of glaucomatous subjects were significantly lower ($p<0{\cdot}02$) at all frequencies but were within one standard deviation of those of the normal controls.

While measurements of contrast sensitivity involve the perimacular region of the retina, classic glaucomatous field loss characteristically occurs more peripherally. Recent work in this laboratory (UW-Madison) reveals a significant association ($p<0{\cdot}05$) between the bilateral asymmetry of Vistech contrast sensitivity scores (at 3 and 6 cycles per degree) and the asymmetry of visual field indices obtained by Humphrey automated perimetry in glaucomatous patients.[14] In the present study, however, asymmetry of Vistech scores between the two eyes did not correlate significantly with the presence of a visual field defect in either eye. Together these studies demonstrate the importance of distinguishing between correlation of contrast sensitivity with glaucomatous change and its actual diagnostic utility.

The use of subjective visual field assessments as the standard for comparison in this study does not preclude the possibility that the Vistech system may elicit some early glaucomatous changes to which perimetry remains insensitive. If so, however, such static contrast changes must occur frequently among normal individuals as well. Thresholding only defective areas in the present study may have slightly reduced the sensitivity of the visual field testing, though a study using the Humphrey Analyzer has revealed differences in subjective interpretation between paired full thresholding and quantification of defects in only 18 of 104 fields.[15] It is possible that modifications of existing contrast sensitivity testing methods may increase their diagnostic utility for glaucoma detection. Such adaptations might include the use of temporal modulation and/or opponent colour contrast paradigms within a rapid and clinically amenable testing format.[13 16–27]

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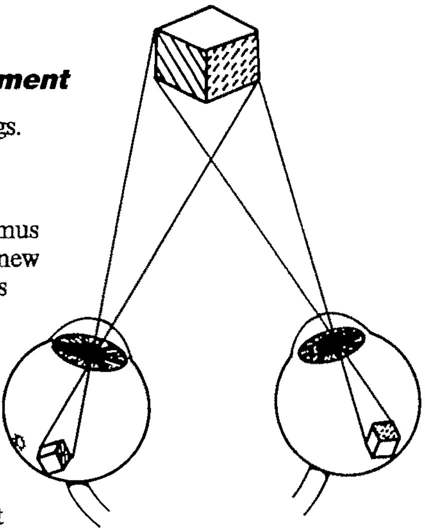

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CASE REPORTS

# In-toto removal of a subretinal *Cysticercus cellulosae* by pars plana vitrectomy

Michiel H A Luger, Jan S Stilma, Peter J Ringens, Joop van Baarlen

**Abstract**

**A case of subretinal cysticercosis was treated with laser coagulations round the cyst prior to surgery. In-toto removal of the living cysticercus was performed by pars plana vitrectomy. Two weeks after surgery 25/20 vision was regained. Histopathology of the cyst confirmed the clinical diagnosis.**

Ocular cysticercosis occurs rarely, but the diagnosis is very important. In most cases untreated intraocular cysticercosis will eventually lead to blindness.[1 2]

The cysticercus is generally found subretinally, but any area of the eye or ocular adnexa may be affected.[1-4] It enters the posterior segment of the eye through the posterior ciliary arteries, reaching the subretinal space. From there the parasite may migrate into the vitreous cavity.

## Case report

A 44-year-old male visited our clinic in January 1990 with a red, irritated left eye and complaints of blurred vision for two months. He had travelled to Indonesia in the summer of 1989.

The visual acuity of the right eye was 25/20. It was entirely normal. On the left the visual acuity was 20/30, motility was normal, and the intraocular pressure was 14 mm Hg. Slit-lamp examination showed a mild conjunctival injection; the anterior chamber had 2+ cells and flare, and the vitreous cavity had 1+ cells. Funduscopy disclosed a subretinal, translucent cyst, 4 disc diameters in size in the superonasal quadrant. A central dense white spot, mobile under bright illumination, indicated the location of the larva inside the cyst (Fig 1). The optic nerve head, macula, and retinal vessels showed no abnormalities.

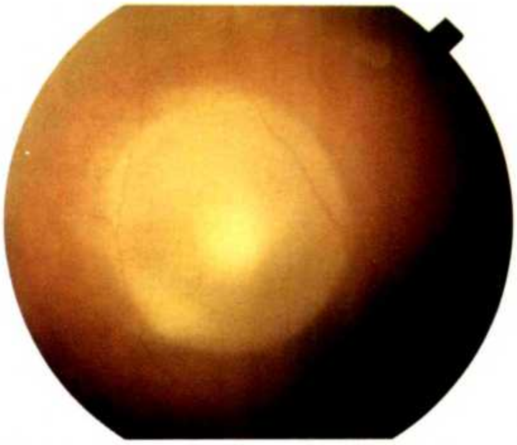

*Figure 1 Fundus photograph showing the subretinal cysticercus. The laser coagulations surrounding the cyst are vaguely discernible.*

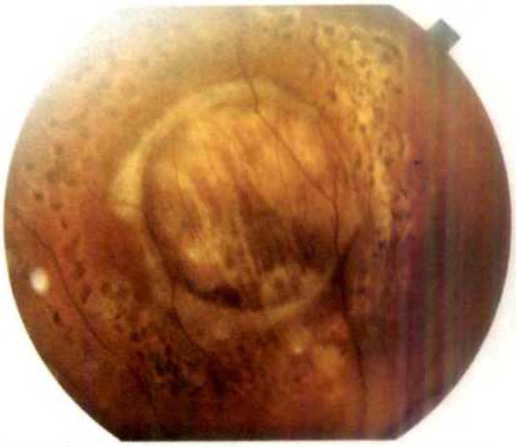

*Figure 2 Fundus photograph two months postoperatively. The optic media are clear and the retina is fully attached.*

Preoperative standardised A-scan ultrasonography revealed two medium to high amplitude echos, indicating a space between the inner cyst wall and the overlying retina. The B-scan showed a subretinal bladderworm with two hooklets.

A general physical and neurological examination gave normal results. The white blood count was normal except for 5% eosinophils. Enzyme linked immunosorbent assay (ELISA) gave positive results for *Taenia solium/Cysticercus cellulosae* immunoglobulins (1:80). Stool specimens, a skull *x*-ray, CT brain scan, and cerebrospinal fluid were normal. There was no evidence of generalised cysticercosis.

Two weeks prior to surgery the subretinal cyst was sealed by surrounding argon laser photocoagulations (wavelength 577 nm, spot size 250 μm, 200 ms, 0·2–0·35 W) (Figs 1 and 2). Systemic prednisone was administered one day preoperatively until one day postoperatively.

An initial attempt to remove the cysticercus by sclerotomy was abandoned because of the location of the cyst underneath a vortex vein. A pars plana vitrectomy was therefore performed. Endodiathermy of the raised retina overlying the

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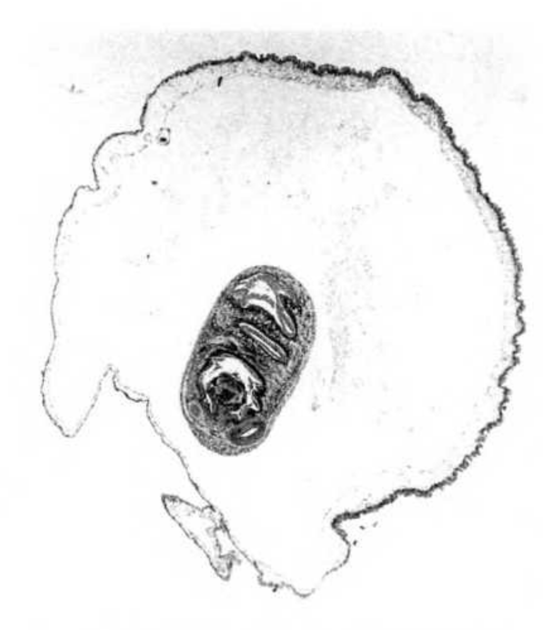

*Figure 3 Histological section of the cyst. (Haematoxylin-eosin, ×30.)*

cyst allowed a safe retinotomy. The cyst was pulled into the vitreous and extracted from the eye in one piece after enlargement of the pars plana incision.

Two weeks postoperatively visual acuity was 25/20 in the left eye, the optic media were clear, the retina was fully attached, and the intraocular inflammation had subsided (Fig 2).

Macroscopic and histological examination confirmed the diagnosis. Within a 3 mm cyst a *Cysticercus cellulosae* larva was found, with several hooks and suckers, conforming to the characteristics of the *Taenia solium* scolex (Figs 3, 4).

## Discussion

*Cysticercus cellulosae* is the larval stage of *Taenia solium*, the swine tapeworm. Human cysticercosis can be acquired when man ingests the eggs of *T. solium*. An intraocular living cysticercus will initiate a foreign body reaction, varying from a mild uveitis to a panophthalmitis. When the parasite is left untreated it will eventually die after two to four years. The accompanying release of toxins induces an inflammatory reaction that may lead to destruction of the eye, though there are exceptions.[1 2 5] Early removal of the cyst is crucial.

The management of subretinal cysticercosis has taken various forms. Antihelminthic drugs, such as praziquantel, are ineffective for intraocular cysticercosis.[6 7]

Xenon and argon laser photocoagulation have been reported to be an efficaceous treatment of small subretinal cysticerci (less than 8 mm).[8 9] Coagulation has the undesired side effect that the dead larva is left inside the eye.[10] Systemic and topical steroids have been reported to suppress the subsequent inflammatory reaction.[1 2 11]

The most effective method of preserving function in an eye with intraocular cysticercosis is surgical removal of the larva. Subretinal parasites can be removed through a sclerotomy.[11-18] But this technique carries some risks. Extensive periocular surgery may be required to gain adequate exposure.[1 2 12 19] Inadequate localisation may lead to non-removal of the parasite. Peroperative migration of the cyst within the subretinal space and migration into the vitreous have been described.[1-3 13 14] Other possible complications are retinal detachment, retinal tear with vitreous loss, vitreous haemorrhage, and bacterial endophthalmitis.

Vitrectomy has been used to remove intravitreal cysticerci.[3 11 13-15 20-22] Steinmetz *et al* reported the successful removal of a subretinal cysticercus after fragmentation of the [illegible] inside the vitreous cavity, using pars [illegible] vitrectomy.[23] This method has several adva[illegible]ages over a classic sclerotomy. The visibility of the parasite during surgery is excellent and the risk of subtotal cyst removal and choroidal bleeding, as in the external approach, is avoided. The risks of a retinotomy can be minimised by preoperative application of delimiting laser photocoagulations (Fig 2). This also prevents peroperative cyst migration within the subretinal space.[8]

The risk of spilling cyst contents is minimal if cutting or aspiration of the cyst can be avoided, as in our case. The presence of a space between the cysticercus and the overlying retina, as demonstrated by our preoperative A-scan ultrasonography, suggests the possibility of removing the cyst in toto.

Intraocular cysts formed by other parasites, such as *Echinococcus* and *Taenia sagginata*, are extremely rare and can only be differentiated from *Cysticercus cellulosae* by histopathology.[1 15 24]

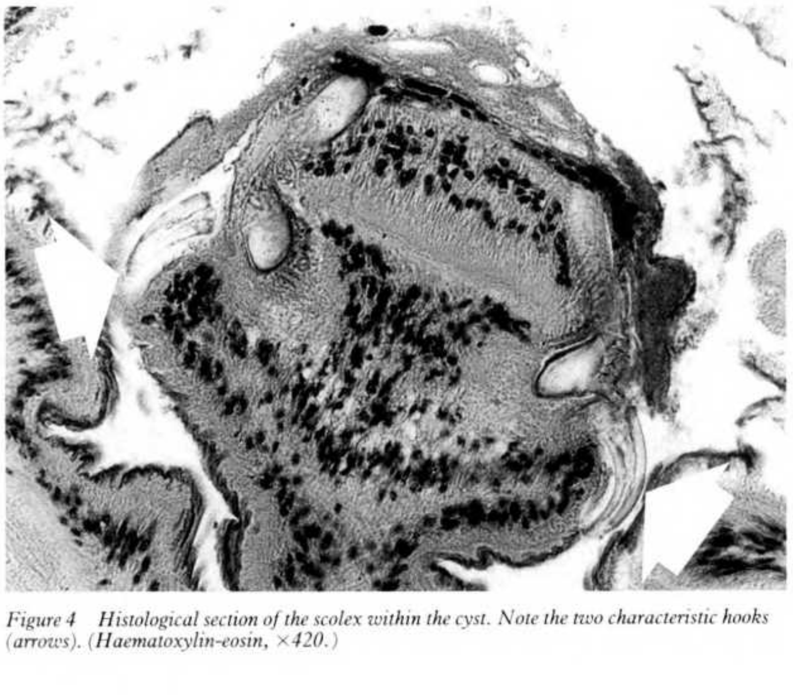

*Figure 4 Histological section of the scolex within the cyst. Note the two characteristic hooks (arrows). (Haematoxylin-eosin, ×420.)*

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*British Journal of Ophthalmology*, 1991, 75, 564

# Spontaneous passage of a dacryolith

Lawrence G Kaye-Wilson

**Abstract**

**A patient had four episodes of recurrent dacryolith over 14 years. Each attack of acutely painful dacryocystitis was terminated by spontaneous passage of the dacryolith. Biochemical and dacryocystographic evidence help to explain the pathogenesis of the condition.**

A 38-year-old woman presented with right-sided epiphora and increasing medial canthus pain of 12 days' duration, unresponsive to topical antibiotics prescribed by her general practitioner. Ocular and medial canthal inflammation were absent. Syringing the lower lacrimal canaliculus resulted in regurgitation of clear fluid via the upper punctum, no fluid reaching the nose. Antibiotic drops and heat applications were advised for presumed low-grade dacryocystitis.

Over the next 24 hours an exquisitely tender medial canthal swelling appeared. This resolved four days later with passage of a hard, dark green, club-shaped dacryolith (Fig 1) into the nasopharynx, which she then spat out. Within two hours pain and swelling subsided and epiphora ceased.

Follow up of the patient 18 months later showed minor watering but maintained patency of the lacrimal passages. Three previous episodes (over 14 years) of similarly treated painful right-sided epiphora were reported. During the 18–24 months before each episode the patient noted slight but gradually increasing unilateral painless epiphora. Each acute attack lasted 7–12 days, pain and epiphora resolving completely and suddenly after she sensed foreign material in the throat. Only eight years previously had the passing material been retrieved, identical in size, shape, and colour to the stone presented on this occasion. She had not previously been examined after an attack. There was no history of abnormal tearing in childhood.

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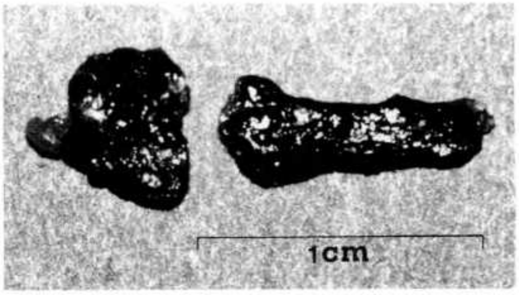

*Figure 1 Dacryolith in two pieces (originally joined, 13·5 mm long).*

INVESTIGATION

Qualitative biochemical analysis of the dacryolith revealed urate, phosphate, and fibrin. No micro-organisms were isolated from the conjunctiva or nose; coagulase-negative staphylococci were grown from the dacryolith. Digital subtraction dacryocystography showed a somewhat dilated lower half of the lacrimal sac and bilateral nasolacrimal duct patency (Fig 2).

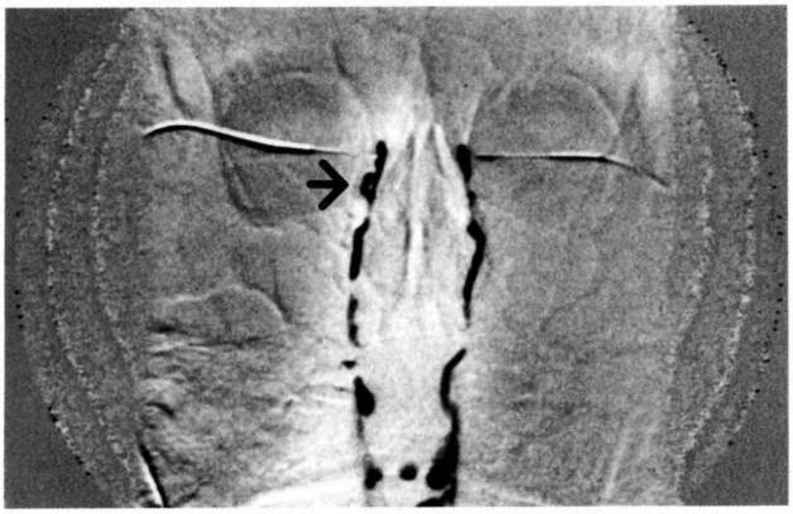

*Figure 2 Digital subtraction dacryocystogram: anteroposterior late phase. Bilateral free drainage of contrast into nasal cavity. Dilatation of lower part of lacrimal sac (arrowed).*

## Discussion

Phosphate is principally an intracellular ion. Urate is derived from cell nuclear purine degradation. This suggests dacryolith formation by slow aggregation of cellular debris over an extended period. Antikeratin antibodies found in a dacryolith[1] support this idea. The stone may have formed in eddy currents in the dilated sac: alterations in channel wall, flow, or fluid explain calculus formation in general. Stone growth (in this case, over two years) causes relative lacrimal passage obstruction and gradually worsening epiphora. Inflammation (hence fibrin) may be due to stagnant infection or irritation by the stone. Clinical dacryocystitis with patency of the nasolacrimal duct also occurs with lacrimal sac diverticuli.[2] Fragmentation[3] and immediate dislodgement[4] of adrenaline dacryoliths by irrigation are described.

At present the patient has insufficient symptoms to warrant further investigation. However, future obstruction is likely, either due to non-passage of recurrent dacryolith or repeated inflammation with resultant fibrotic stenosis. Dacryocystorhinostomy may then be indicated.

I thank Dr I Gillespie, consultant radiologist, Royal Infirmary, Edinburgh, for performing dacryocystography.

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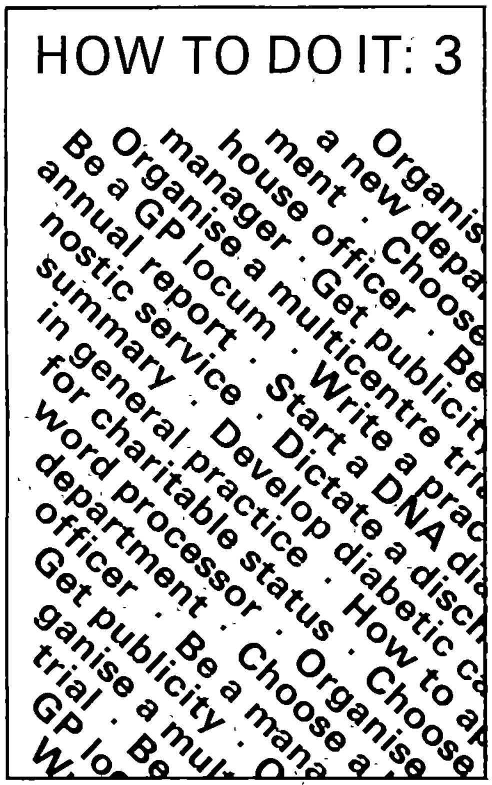

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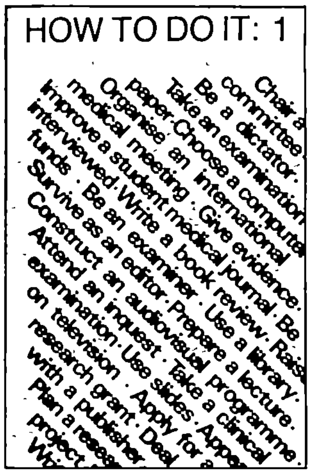

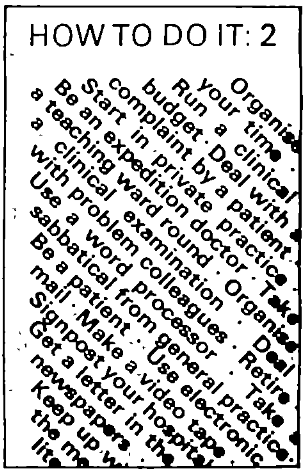

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# *Candida tropicalis* endophthalmitis following penetrating keratoplasty

Wolfgang Behrens-Baumann, Reinhard Ruechel, Ortrud Zimmermann, Martin Vogel

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## Abstract

**A case of *Candida tropicalis* endophthalmitis following penetrating keratoplasty is presented. The donor was an alcoholic, who died of bronchopneumonia and pancreatitis. We presume the candida infection was transmitted by the donor because *Candida tropicalis* was cultured in life from the donor's throat swab and corresponding fungal elements were discovered post mortem in kidney sections of the donor.**

Transmission of infectious agents, including fungi, by donor tissue is a well known complication of corneal transplantation.[1,2] However, there have been only two reports of *Candida albicans* endophthalmitis after keratoplasty.[3,4] This is the first report of an intraocular infection by *Candida tropicalis* following corneal transplantation from a donor with *Candida tropicalis* sepsis.

## Case report

A 76-year-old woman with aphakic bullous keratopathy and high myopia in both eyes, but otherwise healthy, underwent a penetrating keratoplasty on her right eye. The patient received antibiotic ointment before and after surgery and dexamethasone phosphate for the following three weeks. On day 2 and day 10 a vitreous cloudiness was noted, which disappeared subsequently, and the patient was discharged from hospital.

She returned to hospital on day 24 with infiltrates in the inner layers of the donor tissue, white fibrin clots in the anterior chamber, and a leucocoria. Smears from the conjunctiva were positive for *Staphylococcus epidermidis*. Topical tobramycin and systemic cefotaxime were administered without any effect.

On days 35 and 40 after the keratoplasty white intraocular material was removed by vitrectomy. Both aspirates were positive for *Candida tropicalis*. Antimycotic therapy was initiated with daily natamycin ointment and 0·75 μg amphotericin-B injections into the anterior chamber every third day. On day 50 no fungi could be cultured from an aspirate of aqueous humour. Her visual acuity increased to 20/40, and the corneal transplant was centrally clear.

One year later the patient underwent penetrating keratoplasty on her left eye without any complication. The donor of the first keratoplasty was a 54-year-old female alcoholic, who died of bronchopneumonia and pancreatitis. *Candida tropicalis* was cultured in life from a throat swab, and similar fungal elements were discovered postmortem in sections of the kidney by Fungiqual staining. On explantation, the second corneal button of the donor showed white infiltrates and was discarded.

## Discussion

We suppose that in our patient *Candida tropicalis* was transmitted by infected donor tissue, particularly since *C. tropicalis* does not belong to the normal human microbial flora. The predisposition of alcoholics to candidosis is well known.[5] Although the donor did not fulfil the exclusion criteria for donor corneas,[6] the infiltration of the discarded corneal button and the history of alcoholism of the donor should have been a reason for discarding the first cornea which resulted in endophthalmitis. To avoid candidal transmission we suggest that at least immunocompromised donors (including alcoholics) are tested serologically for candidal antigen. Such tests can be performed within 30 minutes in the clinical laboratory. Test kits are available. The tests allow the identification of patients suffering from deep-seated and disseminated candidosis.

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# Retinal vasculitis in a mother and her son with human T-lymphotropic virus type 1 associated myelopathy

S Hayasaka, Y Takatori, S Noda, T Setogawa, H Hayashi

**Abstract**

**A 53-year-old woman had difficulty in walking, raised titres to human T-lymphotropic virus type 1 (HTLV-1) in serum and cerebrospinal fluid, and yellowish white retinal lesions and vasculitis in the right eye. Her 20-year-old son also had difficulty in walking, raised titres to HTLV-1 in serum and cerebrospinal fluid, and retinal vasculitis and multiple whitish vitreoretinal spots in both eyes.**

Human T-lymphotropic virus type 1 (HTLV-1) causes adult T-cell leukaemia/lymphoma (ATLL) and HTLV-1 associated myelopathy (HAM).[1 2] Both conditions are endemic. Cases of ATLL and HAM are prevalent in the Caribbean basin, south-eastern United States, Italy, subsaharan Africa, and Kyushu and Okinawa islands (south-western islands in Japan).[3 4]

Only a few investigators have reported ocular manifestations in patients with HAM living on Kyushu island.[5-7] We examined two patients with HAM living in Izumo (a part of Honshu island).

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## Case reports

CASE 1

A 53-year-old woman complained of difficulty in walking. The disorder was slowly progressive and was followed by spastic paraparesis. Results of routine tests were negative or within the normal range. Raised titres to HTLV-1 in the serum (1:1024) and cerebrospinal fluid (1:32) were found. Myelography, computed tomography, and magnetic resonance imaging showed normal findings. The patient was treated with prednisolone, 100 mg/day; thereafter the drug was tapered to 15 mg/day.

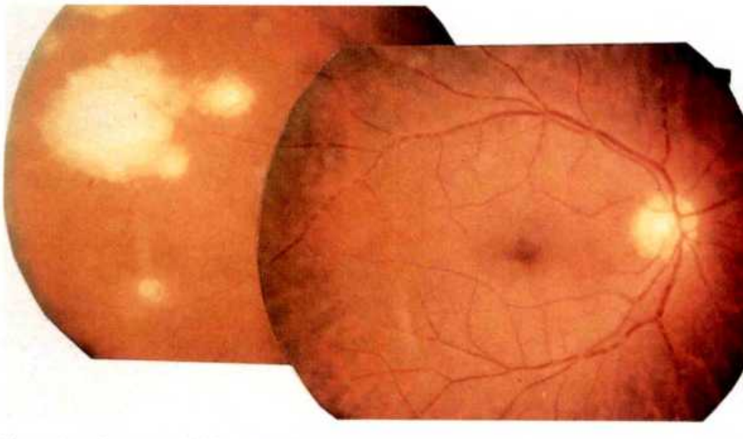

*Figure 1 Case 1: whitish yellow lesions in the right temporal retina and multiple whitish dots round the retinal veins.*

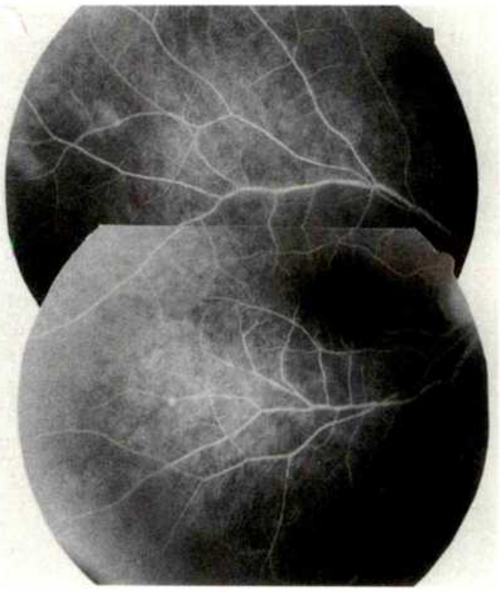

*Figure 2 Case 1: fluorescein angiogram shows that the retinal venous lesions do not leak.*

In July 1990 no retinal lesions were found. In August her right visual acuity had decreased to 20/30. Cells were noted in the right anterior chamber. Whitish yellow lesions were found in the right temporal fundus (Fig 1). In addition multiple whitish dots were noted round the retinal veins. Fluorescein angiography showed that the retinal venous lesions did not leak (Fig 2). Routine laboratory test results were negative or within normal range, including blood pressure; blood glucose level; serum titres to adenovirus, herpes simplex virus, cytomegalovirus, varicella zoster virus, immunodeficiency virus, and toxoplasma; angiotensin-converting enzyme level; IgG; IgM; C-reactive protein; *Treponema pallidum* haemagglutinin; antibody to DNA; antinuclear antibody; rheumatoid arthritis factor; tuberculin skin test; and chest *x* ray findings. No oral aphthae or genital ulcers were noted.

In September 1990 systemic prednisolone, 100 mg/day, diminished the cells in the right anterior chamber but had no effect on the yellowish white lesions or the retinal vasculitis. The prednisolone was tapered again to 15 mg/day. In October the retinal lesions in the right eye gradually diminished. Her right visual acuity improved to 20/20.

CASE 2

The previously healthy 20-year-old son of case 1 complained of problems in walking in October 1989. The disorder was slowly progressive and was followed by spastic paraparesis. Results of routine tests were negative or within the normal range. A small number of atypical lymphocytes were found in his peripheral blood, and raised titres to HTLV-1 were noted in serum (1:8192) and cerebrospinal fluid (1:128). Myelography, computed tomography, and magnetic resonance imaging gave normal findings. No retinal lesions were found. The patient was treated with prednisolone, 50 mg/day. The gait disturbance improved, and the corticosteroid was tapered.

In June 1990 the patient complained of floating spots in both eyes. The corrected visual acuity in both eyes was 20/20. The corneas and anterior chambers were transparent. Small opacities were observed in the vitreous in both eyes. Multiple whitish spots were found in the inferior retina bilaterally. Some lesions appeared around the retinal veins and arteries. Fluorescein angiography showed small amounts of leakage of dye from the vessels. Normal findings were noted on examination of the visual fields, electroretinography, and ultrasonography in both eyes.

Laboratory test results were negative or within normal range, including blood pressure; blood glucose level; serum titres to adenovirus, herpes simplex virus, varicella-zoster virus, cytomegalovirus, human immunodeficiency virus, and toxoplasma; angiotensin-converting enzyme level; IgG; IgM; C-reactive protein; *Treponema pallidum* haemagglutinin; antibody to DNA; antinuclear antibody; rheumatoid arthritis factor; tuberculin skin test; and chest *x* ray findings. No oral aphthae or genital ulcers were noted.

Although the dose of oral prednisolone was increased in July 1990, the retinal spots did not diminish, and the corticosteroid was decreased. In September the fundus lesions gradually went away.

## Discussion

Our patients had myelopathy, a small number of atypical lymphocytes in the peripheral blood, and raised titres to HTLV-1 in serum and cerebrospinal fluid. A diagnosis of HAM was made. Their retinal vasculitis did not respond rapidly to corticosteroid treatment but diminished a few months later. Whitish yellow lesions in the retina of case 1 appeared to be exudate.

The ocular lesions in our patients are probably associated with HAM. Arimura *et al*[5] described abnormal smooth pursuit movements in 11 patients with HAM. Ohba *et al*[6] noted cotton-wool spots in four patients with the disorder. Sasaki *et al*[7] described retinal vasculitis in three patients with HAM. The retinal lesions in our patients were similar to those described by Sasaki *et al.*[7]

Improvement of myelopathy by systemic corticosteroid therapy has been reported.[2] Retinal vasculitis in three patients described by Sasaki *et al*[7] did not respond to corticosteroid treatment. The retinal vasculitis in our patients did not respond rapidly to corticosteroid but diminished a few months later. This may represent either a slower delayed response to corticosteroid or could simply represent spontaneous remission despite the treatment. Mother-to-child transmission has been reported previously in HAM.[8] However, we believe retinal vasculitis in a mother and her son with HAM may be rare.

The present study suggests that antibody titres to HTLV-1 in serum and cerebrospinal fluid of patients with retinal vasculitis should be examined.

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# Orbital squamous cell carcinoma after retinal detachment surgery

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## Abstract

**We report on a 76-year-old patient with a squamous cell carcinoma of the left orbit. The tumour had no connection with the conjunctiva but was located at the site of an encircling band which had been inserted 13 years before. A major part of the tumour presented as a well circumscribed solid mass within the extraocular tissues next to the inferior equator, but the exenteration specimen also showed tumour extension within the adjacent choroid. Histological examination showed a well differentiated keratinising squamous cell carcinoma with numerous mitotic figures and many epithelial pearls. A thorough examination in search of a primary carcinoma of the lacrimal gland or the sinus, with invasion into the orbit, or an epithelial neoplasm elsewhere suggestive of metastatic disease into the choroid did not reveal any specific pathological findings. Thus the most probable origin of the tumour seems to be epithelium which had been misplaced during retinal detachment surgery and had subsequently undergone malignant transformation.**

Among orbital tumours the incidence of squamous cell carcinoma is rather low. It presents mainly as metastases,[1] as an ingrowing sinus or lacrimal sac tumour,[2] and in rare cases as carcinoma of the lacrimal gland[2] or as malignant transformation of a dermoid cyst.[3] Squamous carcinoma of the choroid is likewise uncommon and only known as metastatic disease.[4 5] We present here the clinical and histological features of a patient with co-existing choroidal and orbital squamous cell carcinoma after retinal detachment surgery many years previously and discuss the possible aetiology in this particular case.

## Case report

In September 1975, a 63-year-old non-myopic man presented with bilateral retinal detachment. Both eyes were treated with an encircling band, and visual acuity improved to preoperative values. Follow-up examinations during the next 10 years did not reveal any further fundus abnormalities; both retinae stayed attached.

By 1985 the right eye had developed an advanced cataract, and an extracapsular cataract extraction with insertion of an intraocular lens was performed. The visual acuity (VA) of the left eye at that time was 5/6, the anterior segment being inconspicuous and the posterior segment unchanged. In April 1988 the patient presented with pain and a reduced VA of 2/60 in his left eye. He had suffered from a subretinal haemorrhage in the meantime, which was thought to be responsible for the reduced vision. The intraocular pressure was normal, and there was no evidence of string syndrome such as iris neovascularisation. Artificial tears were prescribed, but a migrainous headache persisted.

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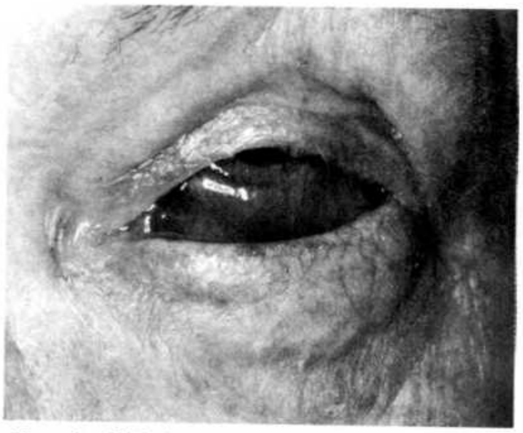

*Figure 1 Clinical preoperative photograph of the patient's left eye, presenting with pain, marked episcleral inflammation in the lower quadrants, upward deviation, and conspicuously restricted movements.*

Eventually, in November 1988, the VA in the left eye had decreased to hand movements, and there was episcleral inflammation in the lower quadrants with upward deviation of the left globe (Fig 1) and conspicuously restricted movement. Now a retinal detachment and a choroidal mass of unknown origin were noted in the peripheral fundus of the left eye near 6 o'clock, whereas the intraocular anterior segment still appeared normal. On ultrasound the posterior wall of the globe was irregularly thickened. A CT scan showed marked calcification at the site of the encircling band, and a nuclear magnetic resonance scan revealed a circumscribed orbital lesion, 10×5 mm, of possibly granulomatous origin between the encircling band and the inferior rectus muscle. At that time a thorough medical examination as well as several blood tests showed no abnormal findings apart from slight hypertension, diabetes mellitus, and zoster of the

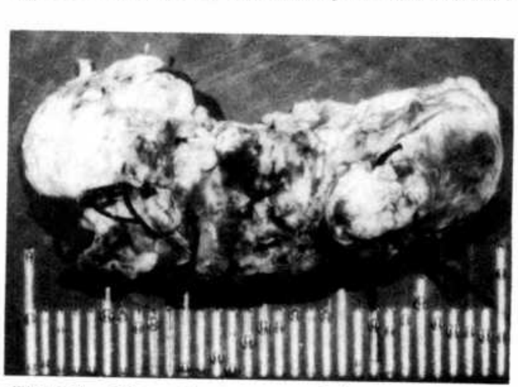

*Figure 2 Microscopic appearance of the removed orbital tumour.*

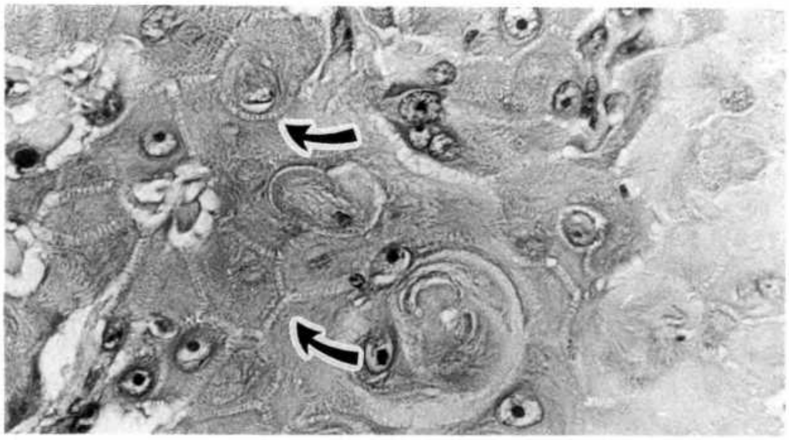

Figure 3A

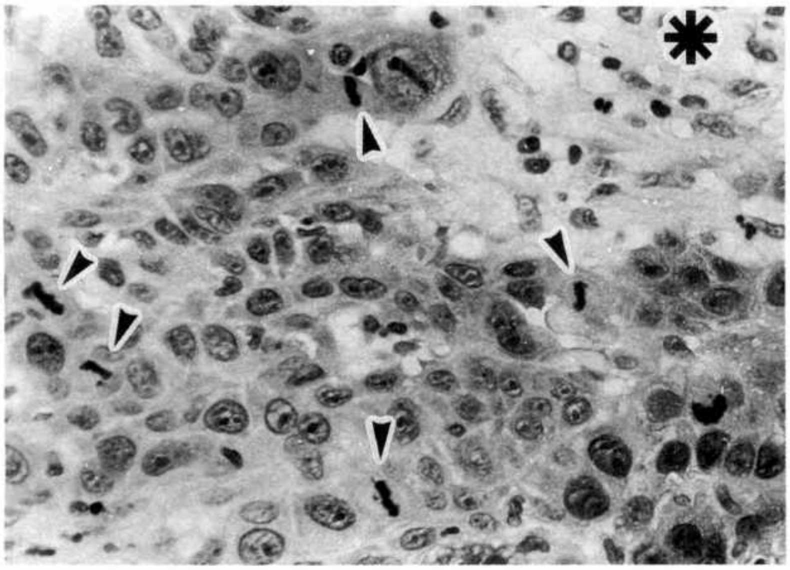

Figure 3B

*Figure 3 Light microscopic appearance of removed orbital tumour. A: Tumour cells at higher magnification, note numerous prickles (arrows). (Haematoxylin-eosin, ×475.) B: Area with undifferentiated cells, several mitotic figures (arrowheads), and inflammatory infiltrates (star). (H-E, ×475.)*

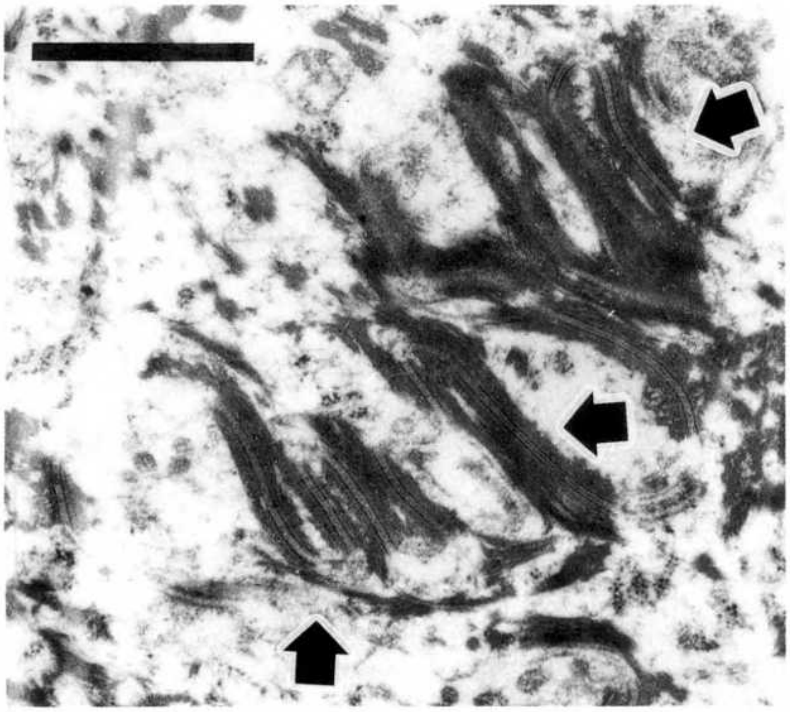

*Figure 4 Electron microscope appearance of removed orbital tumour. Note numerous desmosomes (arrows). (Bar=1 µm.)*

trigeminal nerve. One month later, in December 1988, the encircling band was removed and the tumour seen on nuclear magnetic resonance scan was excised. After histological examination of the excised specimen an exenteration was performed in January 1989.

The patient was last seen in June 1990, when he was well and showed no evidence of tumour recurrence, a primary neoplasm elsewhere, or metastatic disease.

### HISTOLOGICAL FINDINGS

The excised tumour measured 19·5×23·5×12 mm (Fig 2). It was of firm consistency and a whitish colour. Light microscopic examination revealed a keratinising lesion with numerous mitotic figures which was composed mainly of squamous epithelial cells, some of them with definite prickles (Fig 3A). At the periphery the tumour cells seemed to be less differentiated (Fig 3B), and in some parts tumour cells reached the surgical excision line. The connective tissue septa were infiltrated by inflammatory cells. Most tumour cells were arranged in whorls, and nuclear pleomorphism was another prominent feature. Thus the diagnosis of a well differentiated squamous cell carcinoma was made. Electron microscopic investigation confirmed the light microscopic findings, showing typical features of squamous epithelial cells. The tumour cells had irregular nuclei and abundant cytoplasmic tonofibrils with numerous desmosomes (Fig 4) as well as occasional basement membrane formation.

The exenteration specimen was bisected in a vertical plane (Fig 5). Near the superior equator the cavity of the encircling band could be identified, whereas near the inferior equator yellowish tissue had replaced part of the sclera and seemed to join with a pale choroidal tumour (8×3×8 mm) (Fig 5). Microscopically this tumour had similar histological features to those of the previously excised orbital lesion, that is, whorls of keratinising squamous cells with interspersed inflammatory cells (Fig 6). However, more areas of necrosis and more prominent infiltration by lymphocytes and plasma cells were conspicuous. Outside the globe only scar tissue with some granulomatous inflammation and muscle giant cells could be found, but there was no evidence of further tumour tissue. The retina was mostly detached and showed early proliferative vitreoretinopathy. In the area of the encircling band – mainly above – scleral necrosis with marked calcification (Fig 7) corresponding to the findings by CT scan was present. There was also some chronic conjunctivitis, and some strands of normal conjunctival epithelium extended backwards into the inferior orbit towards the site of the previously excised tumour. Otherwise no significant pathological findings could be identified.

Step sections from the exenteration specimen on the nasal and temporal side including the lacrimal gland were free from tumour.

## Discussion

We present here the clinical and histological

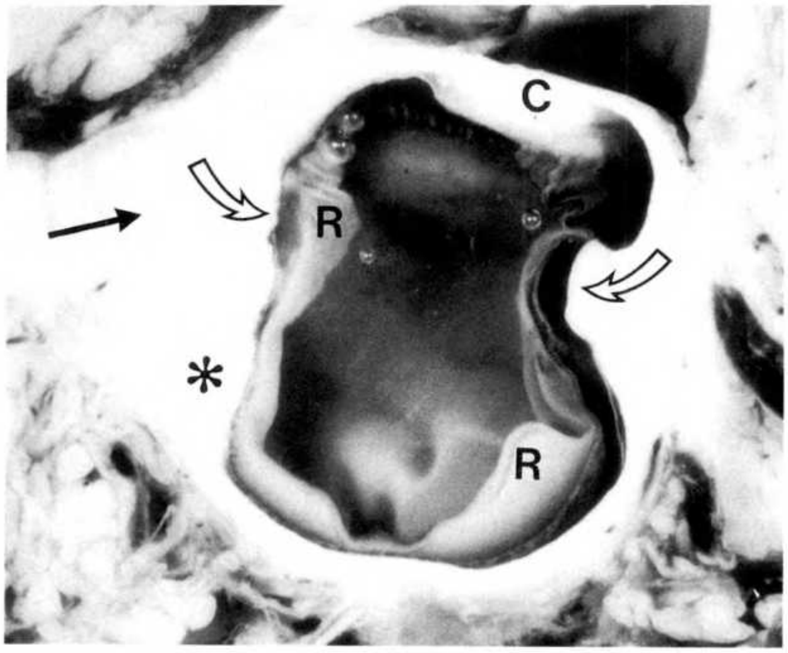

*Figure 5 Macroscopic appearance of exenteration specimen (C=cornea. R=retina. Star=choroidal tumour. Black arrow=site of previous orbital surgery. White arrows=site of removed encircling band).*

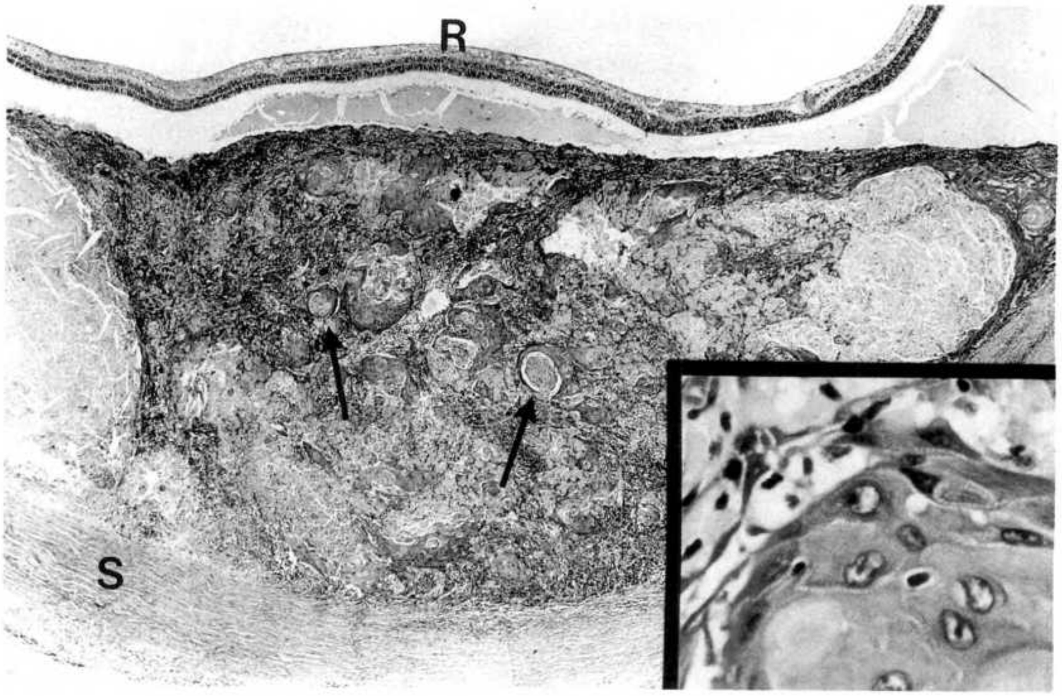

*Figure 6 Light microscopic appearance of choroidal tumour. Note similarity to orbital tumour (Fig 3) with whorls of prickle cells (arrows) but more necrosis and inflammation. (S=sclera. R=retina, posterior pole to the right.) (H-E, ×25.) Inset shows tumour cells with prickles and adjacent inflammatory cells. (H-E, ×500.)*

findings in a patient with an orbital and adjacent choroidal squamous cell carcinoma 13 years after an uneventful encircling band procedure. The diagnosis of a well differentiated highly keratinising squamous cell carcinoma seems to be clear. Since there is no primary squamous cell carcinoma of either choroid or orbit, we have three possible mechanisms to explain its presence.

Firstly, invasion of the orbit by a squamous cell carcinoma from the antrum or frontal sinus has to be considered. The clinical history, the site of the tumour, and its cellular characteristics would be consistent with an extension from the maxillary antrum,[2] but this as well as a lacrimal gland tumour was ruled out by otolaryngological examination, repeated CT scans, and step sections of the exenteration specimen.

Secondly, the possibility of metastatic disease to the choroid from a primary epithelial neoplasm elsewhere with secondary orbital spread has to be investigated. There was, however, no evidence of a primary epithelial neoplasm elsewhere, and in addition the clinical history of pain as a prominent feature, the high degree of differentiation, and the fact that there was more necrosis and reactive inflammation in the choroid than in the orbit favour a primary orbital carcinoma invading the globe. Apart from the apparent absence of a primary tumour elsewhere and the uneventful history of previous tumour surgery, metastasis to the orbit is also unlikely with regard to the site and the histology of the lesion.

Thus the most probable tumour origin (though metastatic disease can never be ruled out completely) seems to be (conjunctival?) epithelium which was misplaced during retinal detachment surgery and subsequently underwent malignant transformation. This would also explain the close proximity of the choroidal/orbital tumour to the encircling band. The conjunctival strands seen on the section are more likely to be the result of recent surgery – that is, the removal of the orbital tumour – since the cells look healthy and normal despite the wrong environment. They do, however, indicate how easily islands of epithelial cells can be displaced deeply into the adjacent tissue.

We are not aware of any comparable case in the literature. In 1986, at the combined Verhoeff Society and European Ophthalmic Pathology Society meeting in Philadelphia, G J Goder presented a case of an orbital squamous cell carcinoma 53 years after enucleation, but he demonstrated continuity of the tumour with the conjunctival epithelium of the socket.

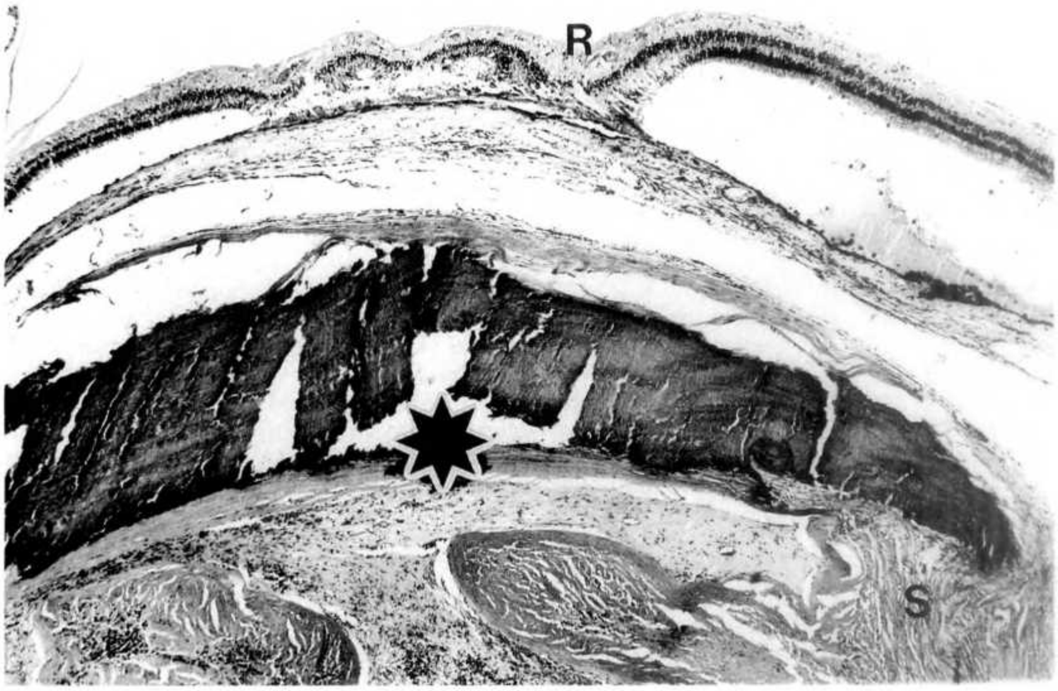

*Figure 7 Calcification (star) at the site of the encircling band. (R=retina. S=sclera. (Periodic acid Schiff, ×50.)*

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# Delayed ciliochoroidal detachment following intraocular lens implantation

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**Abstract**

**Three patients who had extracapsular cataract extractions with intraocular lens implants developed delayed ciliochoroidal detachments, which responded to systemic steroid therapy. This rare complication may have been due to ciliary sulcus fixation of the implant. The possible mechanism and treatment are discussed.**

Delayed ciliochoroidal detachment following cataract surgery is a rarely described complication which may occur some months or years after surgery. The cause is unclear, though trauma, with possible reopening of the section, has been suggested.[1]

We describe three cases which developed approximately nine months after ciliary sulcus fixation of two different types of intraocular lens implants.

## Case reports

### CASE 1

A 63-year-old woman who was generally well underwent an uncomplicated right extracapsular cataract extraction with intraocular lens implantation for a posterior subcapsular cataract. A 21-dioptre posterior chamber Surgidev BUV 20–20 intraocular lens was inserted. There were no immediate postoperative complications. Three weeks after surgery her best corrected vision was 6/6.

Eight months later she presented as a casualty with a one-week history of pain in the right eye. On examination the vision was 6/12+1 with correction. Mild conjunctival injection was present with flare and 2+ cells in the anterior chamber. The intraocular pressure was 1 mm Hg. Gonioscopy revealed an open angle with no evidence of separation of the ciliary body from the scleral spur. On dilatation the intraocular lens was noted to be well centred, though both haptics were in the ciliary sulcus. A small choroidal detachment was present round the entire retina, with some posterior extension inferotemporally. The left eye was normal, with an intraocular pressure of 11 mm Hg.

The patient was admitted to hospital. Oral prednisolone 45 mg daily and topical dexamethasone 0·1% four times a day, cyclopentolate 1% four times a day, and phenylephrine 10% once daily to the right eye were prescribed. Two days later the choroidal detachment had increased, and the anterior chamber was shallow. The eye was padded, and acetazolamide 250 mg four times a day prescribed for three days. The topical steroid was changed to prednisolone acetate 1% two-hourly for the duration of her admission. Four days later the anterior chamber was deeper, though there was no discernible change in the choroidal detachment. The prednisolone was increased to 60 mg daily. On this dosage the patient became restless so it was reduced to its former level after four days, and acetazolamide 250 mg four times a day was reinstituted the following day. Two days later the choroidal detachment appeared the same, the anterior chamber was formed, and visual acuity had fallen to 6/24. Fluorescein angiography showed no evidence of macular oedema. Five days later the anterior chamber was of normal depth, and the choroidal effusion had started to resolve. She was discharged on the same medication.

On review in the outpatient department 10 days after discharge from hospital her visual acuity was normal and the choroidal detachment had resolved completely. Her medications were reduced. Four weeks later all medication had been withdrawn and her visual acuity was 6/6.

Three months after discharge she attended as a casualty again with a sore eye. On examination the visual acuity was 6/7·5, and flare and 1+ cells were present in the anterior chamber. A small inferior choroidal detachment was seen on funduscopy. This resolved on treatment with topical dexamethasone 0·1% and cyclopentolate 1%. There have been no further recurrences.

### CASE 2

A 65-year-old woman, who was fit and well, underwent an uneventful left extracapsular cataract extraction with insertion of a 21-dioptre posterior chamber Rayner Pearce tripod intraocular lens into the ciliary sulcus. Two years before she had had an uncomplicated right cataract extraction with implantation of a similar lens into the capsular bag.

On review six months later her best corrected visual acuity in the left eye was 6/18. Dry macular degeneration was noted. No intraocular inflammation was present, and intraocular pressure was normal. The patient was discharged.

Two months later she presented with a two-week history of photophobia and blurred vision in the left eye. The visual acuity was reduced to 6/24. Moderate flare and 2+ cells were present in the anterior chamber. The intraocular pressure was less than 1 mm Hg, with shallowing of the anterior chamber. On gonioscopy the iris root was displaced forwards by the feet of the implant in the ciliary sulcus, but there was no evidence of a cyclodialysis cleft. On funduscopy a ciliary

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body and 360° annular choroidal detachment were present. The right eye was quiet, with no fundal abnormality apart from early dry macular degeneration.

The patient was admitted to hospital, and oral prednisolone 80 mg daily together with topical dexamethasone 0·1% four times a day and cyclopentolate 1% three times a day to the left eye were prescribed. Five days later the anterior chamber was quiet, and the annular choroidal detachment had almost completely resolved.

The dose of prednisolone was reduced and the patient allowed home. One month later the anterior chamber was still quiet, and there was no sign of ciliochoroidal detachment. The intraocular pressure was 14 mm Hg and her visual acuity had returned to 6/18. All medication was stopped, and on review one month later there was no sign of recurrence.

Six months later the left anterior uveitis recurred. On this occasion the intraocular pressure was elevated at 30 mm Hg, but there was no sign of ciliochoroidal detachment. The condition responded to a three-week course of topical steroid and cycloplegic drops.

### CASE 3

A 74-year-old hypertensive woman underwent an uneventful left extracapsular cataract extraction with insertion of a 20-dioptre posterior chamber Rayner Pearce tripod intraocular lens. Postoperatively it was obvious that fixation was in the ciliary sulcus. The postoperative course was uneventful. Three months after surgery her corrected visual acuity was 6/6, no inflammation was present, and the intraocular pressure and fundus were normal.

Nine months later she presented with a six-week history of mild photophobia and blurred vision in her left eye. Examination of the left eye revealed a best corrected visual acuity of 3/60, mild anterior uveitis, a shallow anterior chamber, an intraocular pressure of less than 1 mm Hg, ciliary body detachment, and a 360° annular choroidal detachment. The choroidal detachment extended posteriorly, inferiorly, and temporally to involve the macula. There was no evidence of retinal detachment. Gonioscopy showed a similar appearance to the iris root to that noted in the second case. There was no evidence of a cyclodialysis cleft. The other eye was entirely normal.

The patient was admitted to hospital. Oral prednisolone 40 mg daily, topical dexamethasone 0·1% four times a day, and atropine 1% twice a day to the left eye were prescribed. After five days the anterior chamber was quiet but the ciliochoroidal detachment remained the same. Consequently the oral prednisolone was increased to 60 mg daily. Over the following three weeks the choroidal detachment gradually resolved; the ciliary body became reattached, the anterior chamber deepened, and the intraocular pressure returned to normal. The patient was discharged on reducing doses of systemic steroids, and four weeks later all medications were stopped. There have been no recurrences, but owing to secondary macular changes the best corrected vision in the left eye remains 6/24.

## Discussion

The cause of delayed ciliochoroidal detachment following extracapsular cataract extraction with intraocular lens implantation is unclear. Trauma with reopening of the wound section has been suggested as a possible cause in some cases.[1] This could result in ocular hypotony and a shallow anterior chamber, with ciliary body and choroidal detachment. In the three cases described above the sections appeared well healed, with no sign of disruption or leakage. The choroidal detachment preceded the flat anterior chamber in the first case, which would be unlikely with wound leakage. Furthermore the choroidal detachments resolved on high-dose steroids, which would be expected to delay rather than accelerate healing of a leaking wound.

A cyclodialysis cleft may cause hypotony and choroidal effusion. Hypotony due to a cyclodialysis cleft has been described as late as 14 months after intracapsular cataract surgery with a medallion clip intraocular lens.[2] It has also been described following rotation of an intraocular lens haptic through a peripheral iridectomy into a cyclodialysis cleft in an eye which had undergone a combined trabeculectomy, cataract extraction, and posterior chamber lens implantation.[3] Hypotony in an eye is one of the main causes of a choroidal effusion.[4] However, in the three cases described there were no signs of a cyclodialysis cleft on gonioscopy, and no peripheral iridectomy was present.

In all three cases the intraocular lens haptics were placed in the ciliary sulcus, and the choroidal effusions resolved on high-dose steroids. Signs of anterior chamber inflammation were also present. Ciliary sulcus fixation in intraocular lens implantation causes a greater change in the blood-aqueous barrier than does capsular bag fixation.[5] In aqueous fluorophotometry the amount of fluorescein appearing in the anterior chamber is significantly greater after cataract extraction with ciliary sulcus lens fixation than with capsular bag fixation.

Disruption of the blood-aqueous barrier could be produced by mechanical contact of a lens haptic with the surfaces of the iris and ciliary body in ciliary sulcus fixation. In capsular bag fixation the intervening capsule may protect these surfaces from contact. This disruption could result in increased permeability of uveal vessels and transudation of fluid from them into the supraciliary and suprachoroidal spaces. This could cause detachment of the ciliary body and choroid, with consequent decreased production of aqueous and hypotony as described by Chandler and Maumenee.[6] The hypotony would produce an increased pressure gradient between the choroidal vessels and suprachoroidal space and thus promote further transudation of fluid into the suprachoroidal space, increasing the size of the effusion.

Steroids have been shown to reduce pathologically raised capillary permeability in a variety of human ocular inflammatory conditions.[7] High-dose oral steroids in these cases may have reversed the disruption of the blood-aqueous barrier and reduced the permeability of the uveal vessels, thus initiating resolution of the ciliochoroidal detachment.

The intraocular lens implant material may have caused inflammation and alteration of the blood-aqueous barrier in the three cases described above. Nylon and polypropylene as used in the haptics of older types of intraocular lenses can activate complement and thus cause intraocular inflammation.[8] Both the Surgidev BUV 20–20 and the Rayner Pearce tripod are made entirely of polymethylmethacrylate (PMMA), which is more inert. However, it has been shown that it can also activate complement.[9] The PMMA lenses used in the above cases may have produced a persistent low-grade activation of complement which may have caused the alteration in the blood-aqueous barrier and intraocular inflammation noted in all three. Steroid treatment, both topical and systemic, would have inhibited the activation of complement.

The delayed occurrence of ocular inflammation and ciliochoroidal detachment in all three cases described above is of interest. The routine topical postoperative steroids could have suppressed an early occurrence, but all the patients had been off medication for at least several months. Two possibilities may account for the delayed response. The intraocular lens haptics might have migrated from their original site and eroded the ciliary body. Ciliary body and iris erosion by PMMA lens haptics and even obliteration of the major arterial circle of the iris have been demonstrated at necropsy.[10] Such erosion would take several months and may be commoner in ciliary sulcus than capsular bag fixation.

The other possibility is that the PMMA in the lens haptics has undergone degradation in the eye, producing a compound capable of initiating inflammation perhaps via the activation of complement. This might take several months to occur and would explain the delay before the inflammation and ciliochoroidal detachment occurred. However, PMMA does not seem to undergo biodegradation. Scanning electron micrographs of intraocular lenses that have bee implanted in an eye for many years show little c no changes in the surface of the PMMA. Indeec when a PMMA Boberg-Ans lens which had bee implanted in a patient for 23 years was compare with an unused lens of the same age by scannin electron microscopy, there was no evidence c biodegradation.[11] It is unlikely that the lenses i the three cases above could have been degradec

To avoid this complication we would sugge that, where circumstances permit, intraocul lens implantation in the capsular bag is prefe able to the ciliary sulcus. Treatment of th condition consists of high-dose oral and topic steroids. If these are ineffective, adding aceta zolamide to the medication should be co sidered. In the first case acetazolamide appeare to aid restoration of anterior chamber depth an may have contributed to the resolution of th ciliochoroidal detachment. Finally, if the cond tion fails to resolve on both topical and system medication, removal of the implant may b necessary.

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# LETTERS TO THE EDITOR

## Glauline (metipranalol) induced uveitis and increase in intraocular pressure

SIR,—I refer to the articles[1,2] in which the observation of uveitis in patients being treated for glaucoma with metipranalol was noted. I wish to report similar findings of uveitis in eight patients being treated with metipranalol, seen at clinics in Wolverhampton and Walsall since March 1990. Of these, five were treated with 0·6% metipranalol, and the remaining three were treated with 0·3%.

The patients being treated with 0·6% metipranalol developed uveitis, with mutton fat keratic precipitates (KPs) and a noticeable pressure rise over the previous visit, when no uveitis was observed. Patients treated with 0·3% developed a less severe uveitis, with mutton fat KPs. A pressure rise was seen in five of the six eyes affected. In all cases the uveitis observed was similar to that of patients with sarcoid uveitis. When the metipranalol treatment was stopped, the pressure dropped and the uveitis cleared in all patients. This was the case even if glaucoma treatment was continued with an alternative β blocker.

A summary of the patients treated and their intraocular pressures is given in Table 1.

Metipranalol was prescribed to approximately 50% of the patients in Wolverhampton and Walsall who required β blocker treatment prior to the notification by Smith and Nephew of the withdrawal of the 0·6% metipranalol. However, no figures are available as to the total number of patients receiving this treatment.

The findings above have been discussed in correspondence with Akingbehin, who confirms that he has made similar observations.[2] Topical metipranalol has now been withdrawn by the manufacturer.

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*Table 1 Summary of patients treated*

| *Patient* | *% Metipranalol at which uveitis detected* | *IOP (mmHg) at visit before uveitis detected (R and L eye)* | *IOP at visit uveitis detected* | *IOP 3 months after metipranalol stopped* |
|---|---|---|---|---|
| 1 | 0·3 | 28, 28 | 28, 32 | 22, 22 |
| 2 | 0·3 | 18, 21 | 20, 24 | 16, 16 |
| 3 | 0·3 | 14, 12 | 22, 22 | 17, 17 |
| 4 | 0·6 | 18, 18 | 22, 22 | 18, 16 |
| 5 | 0·6 | 18, 18 | 38, 38 | 18, 20 |
| 6 | 0·6 | 26, 26 | 24, 28 | 22, 24* |
| 7 | 0·6 | 14, 12 | 26, 26 | 18, 18 |
| 8 | 0·6 | 21, 21 | 34, 16 | 20, 20 |

*Patient 6 developed nummular corneal stromal opacities similar to those produced by adenovirus, causing a red irritable eye, at the same time as the uveitis. These disappeared when the drug was stopped.

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## Broken egg shells of acarine origin on the eyelid margin

SIR,—In the past we have noted the presence of eggs of demodectic mites in debris routinely collected from the eyelid margin in infested patients. In this technique the detritus was gently removed with epilation forceps and placed in a droplet of sterile normal saline on a glass slide and then subjected to light microscopy. The most common egg observed was the shield shaped type characteristic of *Demodex folliculorum* (Fig 1). Only on a rare occasion was the oval contoured egg of *Demodex brevis* seen (Fig 2).

Eggs can also occur on epilated eyelashes along with immature and mature parasites, allowing detailed study of the life cycle. Few observers, however, have witnessed the actual hatching of the egg of this particular acarid. Some years ago Coston noted this phenomenon and left a photographic record of the eggshell splitting to release the larva.[1]

While studying full-thickness specimens of eyelids with scanning electron microscopy we observed broken mite egg shells on the intermarginal strip. The samples were obtained from middle aged patients who had horizontal shortening procedures performed on the lower eyelid. Immediately after resection the specimen was placed in 4% glutaraldehyde solution. It was dehydrated in ethanol and then placed in 100% amyl acetate and critically point dried. The lid specimen was placed on an aluminium stub, gold coated in a Polaron sputter coated with 20 nm of gold, and examined with the scanning electron microscope.

Eggshell remnants were noted on the lid margin as individual broken shield shaped objects. A small number of oval samples were also seen. The majority of specimens were located round the mouth of infested eyelash follicles, displaying protruding tails of demodectic mites. In some areas the cracked eggshells had undergone crenellation.

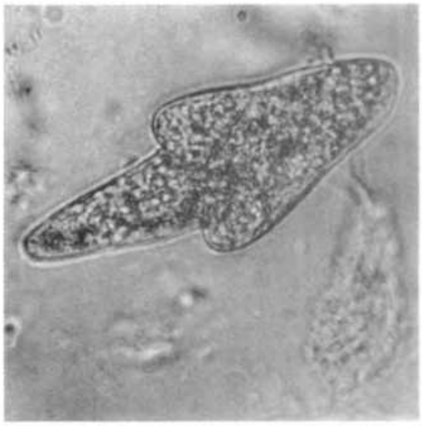

*Figure 1 Shield shaped egg of* Demodex folliculorum. *(× 500.)*

Early in this century Gmeiner[2] measured the live egg and found the length and breadth were respectively 0·08 mm and 0·04 mm. However, in a series of viable eggs we studied the length varied from 0·09 to 0·06 mm. Some shrinkage is also expected in preparing tissues for electron microscopy. It was interesting to note in some specimens the cracked egg shells also possessed two small pyramidal excrescences on their surface consistent with prelarval bosses[3] which are diagnostic of some types of mite eggs.

It is not known if these small particles composed of chitin contribute to those highly reflective foreign bodies sometimes observed on the surface of contact lenses.

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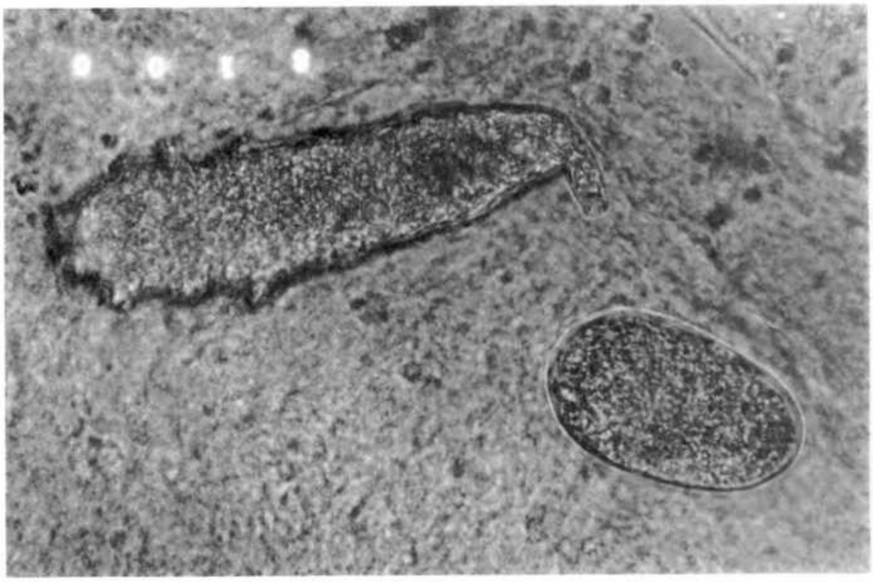

*Figure 2 Oval egg of* Demodex brevis *lying beside the parasite. (× 500.)*

### The ocular pulse

SIR,—The important editorial on the ocular pulse,[1] highlights the observations of the retinal arterial pulsations noted by early ophthalmologists. It was Thiel[2] who first attempted to quantify the recording of the transmitted pulsations which had become known as the tonometric sign as early as 1879. Priestley Smith[3] had clearly described the spontaneous vascular pulsations observed during tonometry. This was reinforced by the observations of Schiøtz and became an important observation for those undertaking tonometry up to the time of the applanation method.

The earliest precise recording of the ocular pulse was that of Thiel in 1928.[2] Subsequently Maurice[4] used a recording tonometer, to be followed by Castren and Lavikanen,[5] who adapted a Muller electrotonometer. Following the work of Suzuki[6] a number of groups developed a system of recording the ocular pulse using a fluid filled suction cup system. The piezoelectric system of Bynke[7] seems to be the least 'invasive' and most precise. The methods of Walker *et al*[8] and Perkins[9] were later developments. In spite of the variety of approaches the amplitude and variation in pulse pressures correlate quite closely. Both in time and form the pulse wave does not correspond with a typical arterial pulsation. It lacks the dicrotic notch which is the characteristic of an arterial pulse, and when placed in time sequence in relation to the R-wave of the ECG, or the Doppler pulse wave recruited from an adjacent orbital vessel, for example, the supratrochlear vessel, its time relationship is closer to the middle of diastole. The only report which demonstrates a dicrotic notch is that of Barnes and co-workers,[10] who applied the pulse sensor, externally, through the lids, and it is believed that this was recording ophthalmic artery pressure pulsations and not an ocular pulse.

While evidence to link the ocular pulse amplitude to either C or PO/C is lacking, there is a significant amount of evidence from all studies that it has a direct relationship with levels of ipsilateral carotid perfusion. The consequence of this is to question the role of a topical β-blocker which does not contain intrinsic sympathomimetic activity (ISA).

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## BOOK REVIEWS

**Aesthetic Surgery of the Eyelids.** By Raul Loeb. Pp 155. Dm 360.00. Springer-Verlag: Heidelberg, 1989.

This book is written by a professor of plastic surgery who specialised in eyelid surgery. It is of interest to the ophthalmologist, as it minutely examines the normal appearance of the eyelids and the anatomical reasons for variation in this normal appearance as well as the pathophysiological changes which occur with age. The ophthalmologist usually concentrates on the functional abnormalities of the eyelids and often does not seek to differentiate the nuances of minor changes in apperarance which can be of great cosmetic significance.

There are chapters on anatomical considerations discussing the variations in bulges in the eyelids; scleral show, which is subdivided into constitutional, developmental, endocrine, and iatrogenic causes; the treatment of excess skin, fat, muscle, and bone; the treatment of depressions, complementary surgeries, and ectropions, and other complications. The author's concepts of recognising depressions in the eyelids and of supplementing deficient tissue with fat grafting or mobilisation are especially interesting. He does not set out to give a standard technical description of how to do a particular operation but rather tries to make the reader aware of the human body's individual variations and how techniques need to be modified to take account of these variations and to avoid complications. All the chapters are copiously illustrated with excellent, clear diagrams and clinical photographs, and there is an extensive bibliography and additional reading section.

Although few ophthalmologists will wish to perform all the procedures described in this book, it is valuable for showing what possibilities exist in cosmetic surgery round the eyelids.

J R O COLLIN

**Manual of Fundus Fluorescein Angiography.** By Amresh Chopdar. (Pp 134; £55.) Butterworth: Guildford, Surrey. 1989.

This book is based on a successful course for ophthalmologists which the author has been running on an annual basis at the East Surrey Hospital. It is divided into 11 chapters and also contains a section for further reading and an index. The first three chapters deal with the basics of angiography and both normal and abnormal fluorescence. The remaining chapters describe the appearances in the more common retinal disorders.

The strength of the book lies in the very high quality of the photographs. Each disease described has a good representative colour illustration with first class clear fluorescein angiograms. Throughout the book there is hardly a plate which is not of excellent standard.

Unfortunately the book is somewhat let down by the quality of the text, not so much in terms of accuracy as of brevity. For instance, topics such as the side effects of angiography are touched on only briefly, and there is no description of their management. No mention is made of stereo photography, which is an integral part of angiogram assessment, particularly of macular diseases. Similarly the clinical descriptions of the various retinal diseases are short and not always accurate. The section on the development of neovascularisation in aging macular degeneration is muddling and the chapter on diabetic retinopathy perfunctory. Some conditions – for example, macroaneurysm, retinal vasculitis, and some of the retinal pigment epitheliopathies – are not described at all.

One has the impression that the book has been written around an excellent set of colour photographs with corresponding fluorescein angiograms. Overall this has generated an excellent primer for readers wanting an introduction to the subject of fluorescein angiography. Since the initial texts published when angiography was a relatively new subject there have been few textbooks on it, and therefore the present volume is to be welcomed. A large amount of angiographic information lies scattered in the ophthalmic literature. This book is useful as an early introduction to the subject in that it draws together the appearances of common retinal diseases. In contrast to the publisher's notes on the cover it is unlikely that the book will be of much value to those retinal specialists looking for more detailed or diverse information.

R H B GREY

**Atlas of Ocular Motility.** By Leonard B Nelson, Robert A Catalano. Pp 228. £60.75. Saunders: London, 1989.

The authors have produced a very comprehensive manual on strabismus. They begin with a detailed account of the anatomy and physiology of the extraocular muscles. There is a thorough description of the tests for visual acuity and binocular function, with an explanation of the underlying physiological basis of Panum's fusional space and stereovision. The standard orthoptic tests are covered in some detail. As a result less than half the text comprises photographs and description of abnormalities of ocular motility. However, in my view the balance is well struck, and the lucid and highly diagrammatic introduction to assessment of motility disorders is followed by well chosen illustrations of the more common conditions, with succinct text. This is an excellent book, which should prove useful as an introductory text for the fellowship candidate and as an approachable reference book.

R A HARRAD

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## NOTE

### Volunteer Eye-Surgeons' Association

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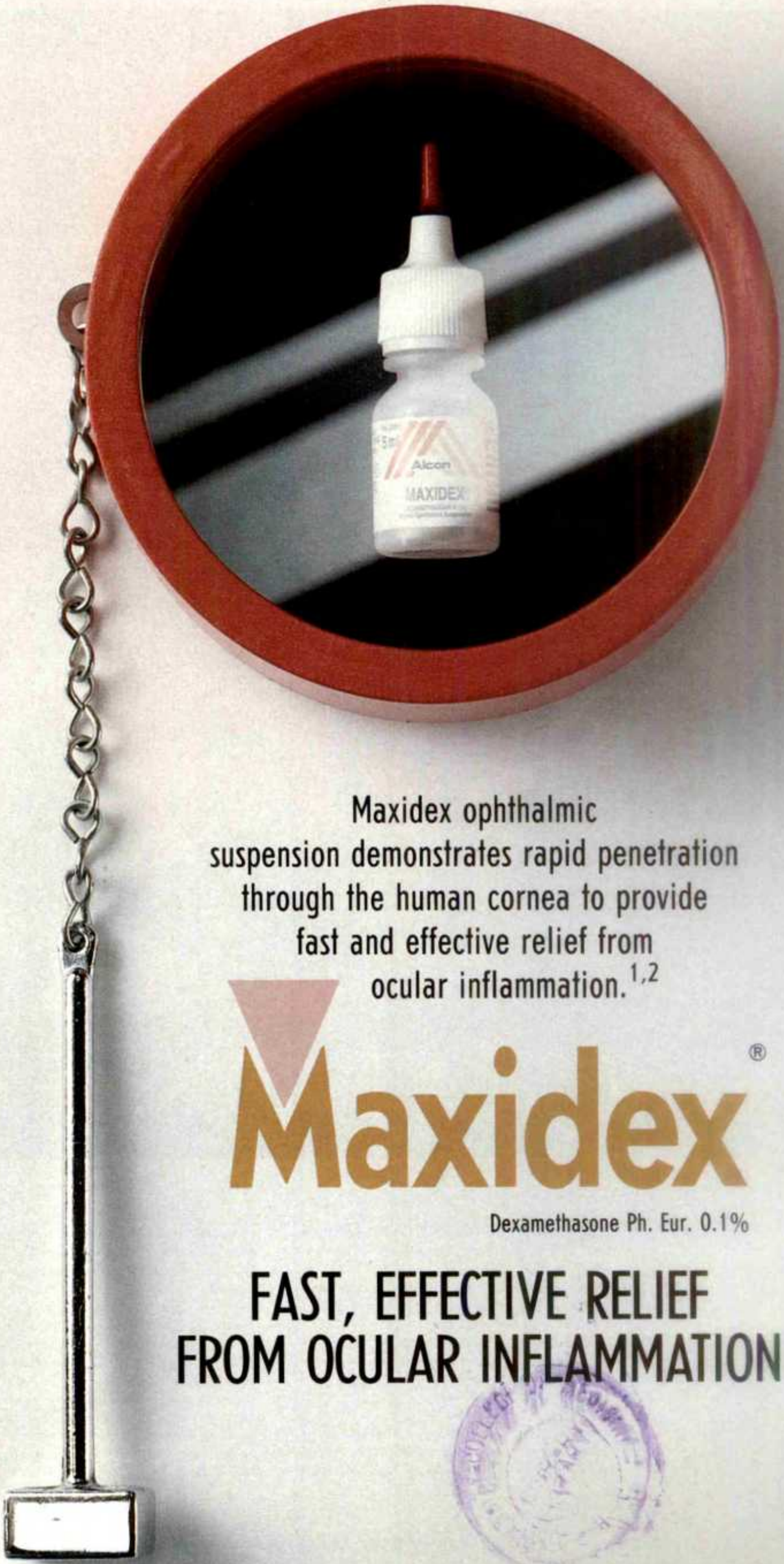

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BRITISH JOURNAL OF OPHTHALMOLOGY

## *Editorial*

# 5-Fluorouracil and beyond

Glaucoma filtering surgery is a very successful method of lowering the intraocular pressure in elderly Caucasian patients. However, groups of patients remain in whom there is a high failure rate following glaucoma filtering surgery, and these include children, Afro-Caribbeans, aphakes, patients with previous conjunctival surgery (including corneoscleral sections for cataract), failed glaucoma surgery, and neovascular glaucoma. The management of this group of patients who fail surgery can pose many problems, and their chances of visual loss increase with every failed procedure.

The failure of glaucoma filtering surgery is usually due to scar formation at the level of Tenon's capsule and the episcleral tissues.[1] This scar formation is associated with the proliferation of fibroblasts in these tissues producing the scar tissue. The initial impetus for the use of antiproliferative agents for ocular scarring came in the early 1980s from Blumenkranz and colleagues investigating the effect of intraocular 5-fluorouracil (5-FU) on the course of proliferative vitreoretinopathy in an animal model.[2] Subsequent studies followed in the tissue culture laboratory to establish the various doses of antiproliferative drugs (including steroids) that would inhibit the proliferation of ocular fibroblasts. Further studies, also from Miami, showed that 5-FU markedly prolonged the survival of the results filtering surgery in an animal model which usually fails rapidly. Patient trials followed with encouraging results, culminating in the recent multicentre 5-fluorouracil filtering surgery study (FFSS) in the United States, in which patients with previous cataract surgery involving conjunctival dissection or failed filtering surgery were randomised to subconjunctival injections of 5-fluorouracil (5 mg) twice daily for the first week and once daily for the second week (a total of 105 mg).[3] In the control group 50% of the eyes had failed surgery at one year (intraocular pressure greater than 21 mm Hg or a reoperation) compared with only 27% in the group that received 5-FU.

However, 5-FU does have complications. Corneal epithelial toxicity and conjunctival wound leaks are commoner after 5-FU, and these side effects may persist even after 5-FU has been stopped. In the FFSS 44% of the patients did not receive all the injections, mainly because of these problems. Other complications in the 5-FU group that did not occur in the control group included a bacterial ulcer that led to perforation in an eye with pre-existing corneal oedema. Other cases of severe corneal complications following 5-FU have also been reported, all in eyes with pre-existing corneal pathology. 'Spontaneous bleb rupture' occurred in 7% of the patients, and many of the blebs following 5-FU are thin and cystic. Whether this will lead to a higher incidence of endophthalmitis in the long term remains to be seen.

Lowering the total dose of 5-FU to about a third of that given in the multicentre trial, delaying the first injection, and adjusting the frequency according to the clinical response seem to reduce the side effects without affecting the success rate. Nonetheless, epithelial defects still occur with these lower doses and so do failures. In addition the daily injections are inconvenient for the patient and may be uncomfortable. Where do we go from here?

The incorporation of 5-FU and other antimetabolites into substances that delay release such as liposomes, collagen and polymers, which can be implanted locally at the time of surgery, may overcome the problems of injections. In theory it is also possible that the slow release of lower levels of antimetabolites may result in fewer side effects. However, disadvantages include an inflammatory reaction to these slow release agents, extrusion of the implants, and the requirement for surgical removal if side effects are excessive. Many other antiproliferatives have been tested which show promise, such as cytarabine (whose effects on corneal epithelial cells may be blocked by 2′-deoxycytidine), and taxol, which interferes with the cytoskeleton. Another novel approach is the use of monoclonal antibodies to receptors which are expressed in the proliferating cell, linked to a cellular poison which leads to the preferential killing of the proliferating cell. However, these agents are still experimental, and clinical use may reveal many other side effects. Before we continue on a relentless march looking for new antiproliferatives we need to remember that 5-FU was first synthesised in 1957 and yet only used after filtering surgery nearly 30 years later. β-Radiation, which has been used in opthalmology for more than half a century, may well prove to be a valuable ally in the prevention of scarring after filtering surgery, particularly because of the simplicity of application and the lack of side effects compared with 5-FU.

Apart from the inhibition of fibroblast proliferation other avenues of treatment include inhibiting the formation of or dissolving fibrin, which provides the scaffold for scar formation, or the prevention of collagen crosslinking with agents such as β-aminopropionitrile, which improved the success rate when given topically to patients after filtration surgery. Whether these agents alone or in conjunction with an antiproliferative drug can provide a higher success rate with fewer side effects remains to be seen.

There are, however, still many unanswered questions about the processes following filtering surgery that lead to successful aqueous drainage. For instance, why do children[4] and Afro-Caribbeans[5] undergoing primary surgery have a higher failure rate? What is different about the cellular mechanisms of wound healing in these groups? The relatively empirical use of antiproliferatives to inhibit fibroblast proliferation provides us with a partial solution, but it is important that the basic mechanisms underlying the healing processes and the flow of aqueous that follow filtering surgery are identified.

There is now evidence that early filtering surgery reduces visual loss.[6] In addition, the concept that intraocular pressure should be reduced to as low a level as is safely possible is gaining wider acceptance.[7] As such, we need to identify the individual tissue and cellular factors that control the healing response and the flow of aqueous after filtration surgery not just in high risk patients but in all patients undergoing filtration surgery, so that we can ensure a successful and significant long term lowering of intraocular pressure.

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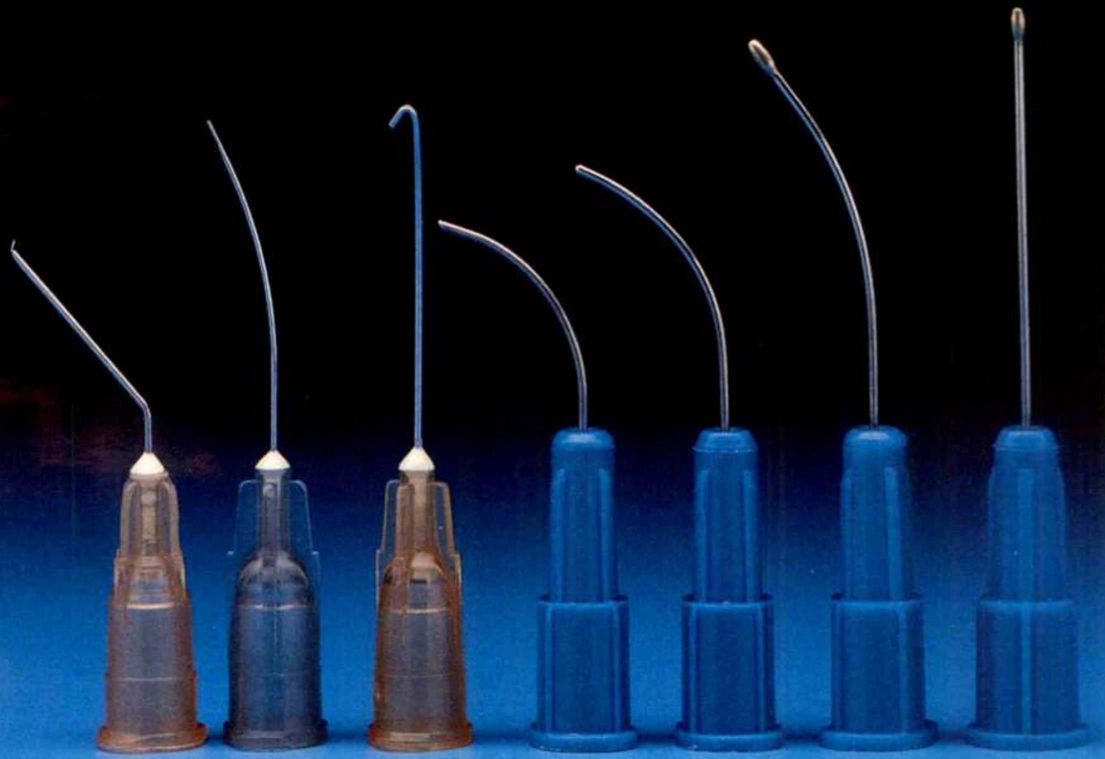

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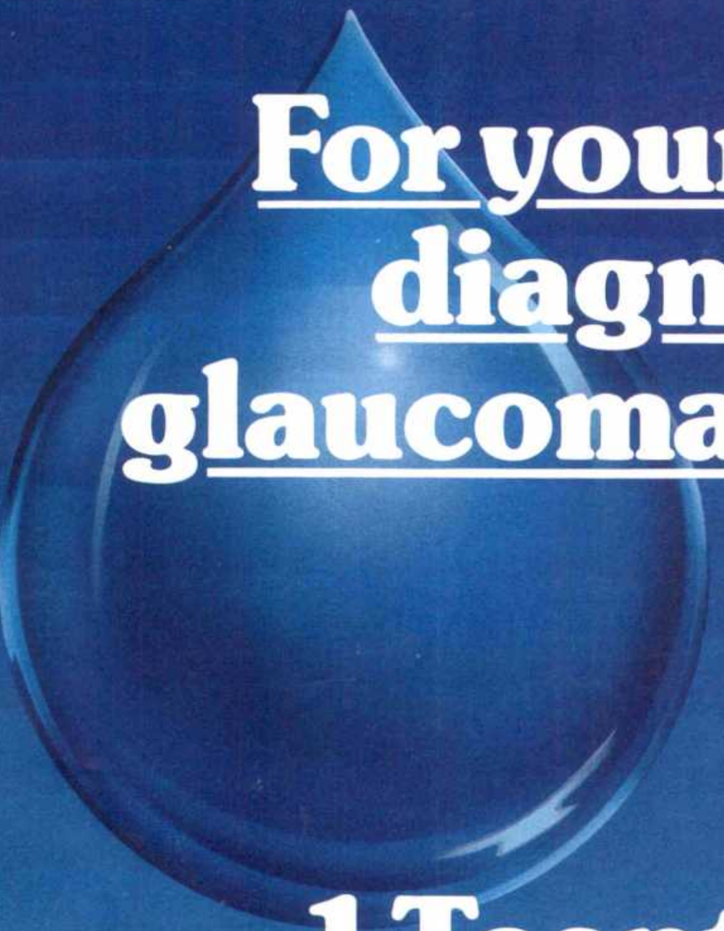

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*British Journal of Ophthalmology*, 1991, 75, 579

# *Editorial*

## Anterior segment malformations: aetiology and genetic implications

New theories in science and medicine seem to gain wider recognition if they are seen to be controversial and to threaten to demolish their predecessors. Often, however, the novelty appears in retrospect to be less substantial and due more to semantic change.

In 1966, Reese and Ellsworth published a paper entitled 'The anterior chamber cleavage syndrome'[1] in which they attempted to group together several anomalous conditions of development of the front of the eye. In so doing they were aware that the concept which they termed 'faulty cleavage' as applied to Axenfeld's anomaly, Peters' anomaly and Reiger's anomaly might be misunderstood. They anticipated later criticism by affording it a wide definition so as to include 'all possible factors such as improper differentiation, absorption and even shifting or mobilisation of tissue in its developmental stage'. Despite this breadth of meaning given to the term, the word 'cleavage' itself failed to convey all that the authors intended, and a misconcept of it was remembered.

This made it easier for the next major synthetic theory, proposed by Kupfer and Kaiser-Kupfer, to gain attention.[2] In this the novelty was not so much to counter the idea that cleavage occurred to produce the angle structures of the anterior chamber as that the tissues which develop therein are formed from cells of neural crest origin. It was already known that three waves of mesodermal cells, later called mesenchyme, invaded the surface ectoderm during the formation of the cornea, but these authors cited marker studies in evidence for an origin in the neural crest. In this way abnormality of neural crest cells could be a cause of the various developmental defects described.

There are two strong reasons for emphasising this. The first was that it allows the idea of a cell type, with a possible genetic defect, failing to develop and differentiate normally in its destination site, such as the iris stroma or the trabecular meshwork. The second was that it provided an explanation of the coincidence of other abnormalities such as dental and facial defects seen in many cases of anterior eye anomaly.

Many subsequent reports have linked genetic and chromosomal defects with anterior segment malformations of the eye. In the paper presented in this issue by Holmström and colleagues evidence is given for the possibility in some cases of a gene defect with an autosomal dominant inheritance. The variation in abnormality in affected family members is presumably due to variable expression of the gene. They point to a particular problem which derives from this variability, which is that some of the offspring of mildly affected mothers were severely affected. This was not to be expected because of the absence of extraocular defects, and so, without the knowledge that a dominant gene was responsible accurate predictions of risks to offspring could not be made.

Work on the human genome, as on the Channel Tunnel, continues relentlessly and will eventually produce dramatic results. The pace of progress in genetics is particularly impressive. In the past decade the number of loci which have been mapped to specific chromosomes has risen from a few dozen to approximately 2000. In the same period the number of gene probes which may be used in linkage studies has reached over 5000.[3] It is likely that we shall not have to wait long for a gene probe for Reiger's syndrome. This will then provide the opportunity for prenatal identification of affected individuals and improved genetic advice. In the meantime, and in any case, the clinician dealing with an infant with anterior ocular malformation must remember to inquire fully into the family history and examine the eyes of the parents and siblings. He should then refer to a paediatrician to exclude other defects such as dental, heart, and limb deformity and deafness, as well as seeking the advice of a clinical geneticist, as an integral part of the management of the eye disorder and its complications.

R M L DORAN

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ORIGINAL ARTICLES

# Effect of β radiation on proliferating human Tenon's capsule fibroblasts

P T Khaw, S Ward, I Grierson, N S C Rice

## Abstract

**The effects of different doses of β radiation from a strontium-90 source on the proliferation of human Tenon's capsule fibroblasts were studied. The cultured fibroblasts were exposed to doses of 100, 250, 500, 750, 1000, 1500, and 3000 rads, and cell numbers were counted at days 3, 7, and 14. Treatment inhibited the proliferation of the fibroblasts. At seven days the cells exposed to 3000 rads showed a decrease relative to the starting cell numbers, and at 14 days the cells exposed to 1500 and 3000 rads showed a decrease in cell numbers. The doses of radiation which inhibited cell proliferation more than 50% (at day 7 and 14) and yet did not cause a decrease in the cell population were 500, 750, and 1000 rads. β Radiation reduces the proliferation of human Tenon's capsule fibroblasts, and at higher doses this effect may be more pronounced one and two weeks after irradiation.**

Filtering surgery is a highly successful procedure in elderly Caucasian patients.[1] It lowers intraocular pressure more than medical treatment[2] and may be superior in terms of preservation of visual function.[3] However, some groups of patients have a high risk of failure from filtering surgery. They include patients who have had previous conjunctival surgery or trabeculectomy,[4] aphakes,[5] patients with neovascular glaucoma, children,[6] and Afro-Caribbeans.[7] The use of postoperative subconjunctival injections of the antiproliferative agent 5-fluorouracil given over two weeks postoperatively has enhanced the success rate of trabeculectomy but has been associated with side effects such as corneal erosions and opacification, thin leaking blebs, and hypnotonic eyes.[8 9] In addition the regimen of injections, even in its simplified forms, is still inconvenient and poses practical problems of delivery in children and in rural areas of Africa where trabeculectomy may be the only feasible treatment.

The failure of filtering surgery in animals[10 11] and humans[12 13] is associated with scarring at the level of the subconjunctival and episcleral tissues. This is associated with cellular proliferation, particularly fibroblast proliferation.[11 13 14] Ionising radiation has been used to inhibit ocular cellular proliferation, particularly after pterygium resection.[15 16] Although there have been studies on the efficacy of postoperative β radiation after filtering surgery,[17-20] there have been no large controlled studies, and the reports of efficacy have been variable. In this unit 750 rads of β radiation from a strontium-90 source have been used after filtering surgery in children for the last eight years. The dose of 750 rads was chosen because of long experience with this dose on pterygia.

The effects of β radiation on filtering surgery in rabbits have been studied, and Miller *et al*[20] found that a single dose of 2500 rads prolonged bleb survival in the rabbit, which displays very aggressive healing. Nevarez *et al*[21] investigated the effect of β irradiation from a linear accelerator and a strontium-90 source on monkey Tenon's capsule fibroblasts in tissue culture over the course of a week. However, the wound healing in the monkey eye is also more aggressive than in the human.

We performed this study to ascertain the effects and dose responses of human Tenon's capsule fibroblasts to β radiation from the strontium-90 source used in our clinical practice.

## Materials and methods

Pieces of redundant Tenon's capsule were obtained from a 2-year-old child during surgery. They were placed in 25 cm$^2$ tissue culture flasks and grown in Hams F10 (Gibco, Paisley, UK) supplemented with 10% fetal calf serum, amphotericin B (0·25 mg/l), penicillin (100×10$^3$ IU/l, and streptomycin (100 mg/l) and incubated in a humidified mixture of 5% $CO_2$ and air at 37°C. The cells were passaged 1:3 and used at fouth passage. The cells were seeded at a density of 2500 cells/well in four wells of 96 well plates. Three groups of 96 well plates were used with eight plates in each group.

The wells were 55 cm apart to minimise the chance of any scattering of radiation to adjacent wells. The cells were allowed to incubate and settle for 24 hours. The medium was then replaced with Hams F-10 buffered with 25 mM HEPES and the culture plates were transported to the radiation therapy room. Each plate was kept out of the incubator for the same length of time. The centre of each well was then placed in contact with the centre of the strontium-90 applicator, which covered the entire surface area of the well. The calibration certificate issued with the probe was used to calculate the exposure time for each well. The dose rate for the applicator was 4·8 rads/s. Doses of 100, 250, 500,

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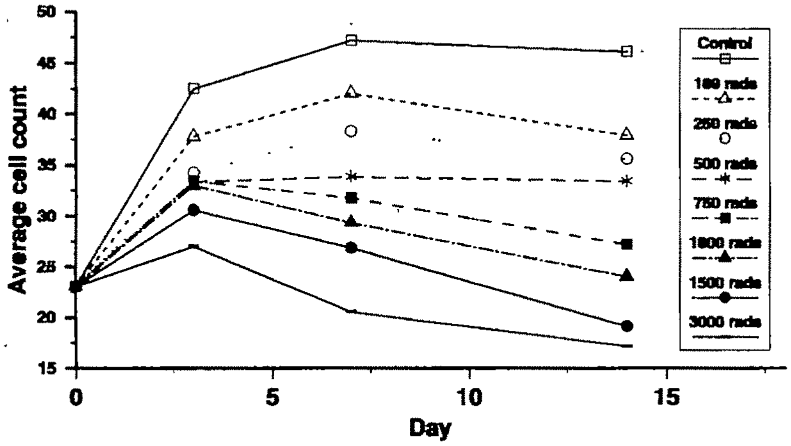

*Figure 1 Average cell count at days 0, 3, 7, and 14 after treatment with different doses of radiation.*

750, 1000, 1500, and 3000 rads delivered to the appropriate wells. After treatment the control and irradiated cells were returned to the laboratory, where they were fed with fresh F10.

Then at day 0, day 3, day 7, and day 14 the appropriate wells were rinsed gently with phosphate buffered saline, fixed with ethanol, and stained with haematoxylin. The number of cells in a field 0·75×0·55 mm were counted, and this was repeated in different areas of the well 10 times for each well (approximately 13% of the total well surface area). The average count for each well was then calculated, and the average and standard deviation of the four wells were then calculated and used for statistical analysis. This method was used because preliminary experiments in our laboratory had shown it to be more consistent and accurate than Coulter or haemocytometer readings when dealing with small numbers of cells.

The results were analysed by analysis of variance, and confidence intervals were derived for the different doses at each time interval. Regression analysis was also used to calculate the trend with increasing radiation dose for each day, by means of Minitab statistical software (Minitab Corporation, USA).

## Results

There were no statistically significant differences between the groups before treatment. However, three days after treatment the control cells had proliferated significantly more than the treated cells, and this trend continued for days 7 and 14. At the highest two doses of 1500 and 3000 rads there was actually a fall in the total number of cells in comparison with the starting number of cells (Fig 1).

```
------+----------+----------+---------+
                          (----*---) Control
              (---*---)  100 rads
         (---*---)       250 rads
     (----*---)          500 rads
     (----*---)          750 rads
     (---*----)         1000 rads
 (----*---)             1500 rads
(----*---)              3000 rads
------+----------+----------+---------+
   28.0      35.0      42.0      49.0
 CONFIDENCE INTERVALS FOR CELL COUNTS: DAY 3
```

*Figure 2 Individual 95% confidence intervals for mean based on pooled standard deviation.*

```
--+---------+---------+---------+----
                           (-*--) Control
                      (--*-) 100 rads
                  (-*--)     250 rads
             (--*-)          500 rads
           (--*-)            750 rads
         (-*--)             1000 rads
      (--*-)                1500 rads
(--*-)                      3000 rads
--+---------+---------+---------+----
20        30        40        50
 CONFIDENCE INTERVALS FOR CELL COUNTS: DAY 7
```

*Figure 3 Individual 95% confidence intervals for mean based on pooled standard deviation.*

At day 3 the untreated control cells had proliferated significantly more than the treated cells, but within the treatment groups only the 1500 and 3000 rad treated cell were different from the 100 rad group. For days 7 and 14 the spread within the groups increased, and at day 14 the groups could be divided into those treated with 100, 250, and 500 rads, those receiving 750 and 1000 rads, and those treated with 1500 and 3000 rads, which were statistically distinct from each other.

The statistical difference between the various radiation groups is represented graphically in Figs 2, 3, and 4 by one-way analysis of variance and plotted confidence intervals. If the confidence level bars do not overlap, the difference in count is statistically significant at the $p<0{\cdot}05$ level.

Cell proliferation decreased relatively to the control when cells were treated with increasing radiation doses, and this effect was more pronounced at days 7 and 14 than on day 3. This is best illustrated by plotting the cell proliferation as a percentage of the control population (Fig 5). Regression analysis showed a decrease in proliferation with increasing radiation dose that was significant at the level of $p<0{\cdot}0001$ for all three days. The change in cell proliferation for each dose of radiation at days 3, 7, and 14 was significant only at doses of 750 rads or more ($p<0{\cdot}05$, analysis of variance).

The doses which inhibited proliferation more than 50% ($ID_{50}$ level) and yet did not cause a fall in the overall number of cells were 500, 750, and 1000 rads. For the groups treated with 3000 rads at day 7 and those treated with 1500 and 3000 rads at day 14 there was an actual fall in the cell numbers below the number in the wells originally.

Morphologically the untreated fibroblasts maintained a relatively spindle shaped appearance. At increasing doses of radiation the cells became more polymorphic. At doses between 500 and 1000 rads there was more variation in cell size, with some large irregularly shaped cells.

```
-----+---------+---------+---------+-
                            (-*-) Control
                    (-*-)  100 rads
                 (--*-)    250 rads
               (-*--)      500 rads
         (-*-)             750 rads
      (-*-)               1000 rads
  (-*-)                   1500 rads
(-*--)                    3000 rads
-----+---------+---------+---------+-
    20        30        40        50
 CONFIDENCE INTERVALS FOR CELL COUNTS: DAY 14
```

*Figure 4 Individual 95% confidence intervals for mean based on pooled standard deviation*

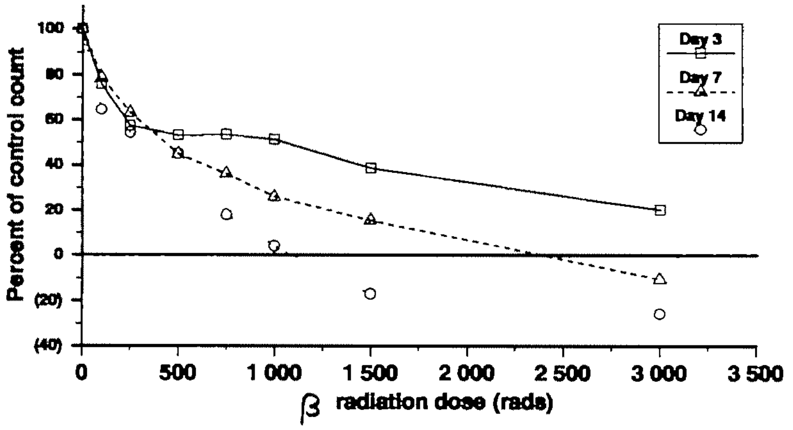

*Figure 5 Fibroblast proliferation at days 3, 7, and 14 in relation to control.*

At doses of 1500 and 3000 rads the cells were mostly small and irregular, with noticeably more cells floating free in the media.

## Discussion

The inhibition of fibroblast proliferation is associated with an increased success rate following filtration surgery.[4] From the results of this study the use of β radiation clearly inhibits the proliferation of human Tenon's capsule fibroblasts. The optimum dose for retarding this fibroblast proliferation by more than 50% but not causing a decrease in the cell population over 14 days seems to be between 500 and 1000 rads. The effects of the different doses are more marked at day 14 and day 7 than at day 3, particularly at the higher doses of radiation from 750 rads upwards. At day 7 for the cells treated with 3000 rads there is actually a fall in the total number of cells, and this occurs at day 14 in the cells treated with 1500 and 3000 rads. This fall in cell number is probably due to severe damage and death in some fibroblasts, resulting in detachment of the cells from the tissue culture plate. This may be important clinically, as marked cell death may stimulate inflammation, which may result in further scarring.

This was unlike the study of Nevarez *et al*[21] using monkey Tenon's fibroblasts, where 3000 rads did not result in a significant decrease in the cellular population in comparison with 1500 rads at either day 3 or day 7. There was also a statistically significant recovery of the monkey cells treated with 100 rads between day 3 and day 7, unlike our experiment. This could be due to different responses of animal and human cells, but there are many other factors which must also be considered such as different culture media, cell passage number, and actual cell variations which may occur within species.

How long the trend of a prolonged effect on proliferation would continue is unknown. The long term effects of radiation on the resident fibroblast proliferation are important, as it is well known clinically that radiation may affect wound healing for at least several months after radiation treatment.[22 23] Failure of filtering surgery, though most common in the first few months, may persist several years after surgery,[13] and any long term effects on the local fibroblasts may be important. This aspect of antiproliferative treatment is being investigated further in our laboratory.

Experiments with tissue culture obviously have limitations. This experiment was performed on a monolayer of proliferating Tenon's fibroblasts, which may be more sensitive to radiation than non-proliferating cells in Tenon's capsule in the body. In the clinical situation the radiation is given directly postoperatively when the majority of fibroblasts are not actively proliferating and the radiation would be expected to have less effect on the cells.[24] However, the transcription of certain genes which are closely associated with the initiation of cell proliferation has been shown to increase markedly within 15 minutes of exposure to growth factors. These growth factors include platelet derived growth factor, which is released in abundance shortly after tissue is injured.[25] It is of interest that one study found immediately postoperative β irradiation to be more effective in preventing recurrence of pterygium than β irradiation given four days after surgery.[26]

Radiation has been given in divided doses after ocular surgery and is easily performed after filtration surgery in adults. However, divided doses of radiation are not easily given to young children. The optimum regimen for postoperative β irradiation is unknown, but this experimental model may be helpful in determining any fractionation of treatment.

The doses delivered to the cells in this model and in vivo are also not exactly the same. The cells in culture are monolayers with a layer of plastic between the cells and the strontium-90 applicator. In the in-vivo situation the fibroblasts are distributed throughout Tenon's capsule and in the sclera beneath. However, plastic is a good tissue model because β radiation is attenuated as in human tissue, and the thickness of the tissue culture plate approximates to the thickness of the conjunctiva and Tenon's capsule in children at the time of irradiation during surgery.

The size of the strontium-90 applicator may have some bearing on the clinical effect of the β radiation. The cell culture wells used in this experiment were smaller than the applicator and as such received a consistent dose of radiation. However, in clinical practice the β radiation is fairly localised to the region under the applicator. Fibroblast recruitment by cell migration may occur from regions of Tenon's capsule adjacent to the applicator, and peripheral scarring may restrict the area available for aqueous drainage. This is not the case in subconjunctival injections of 5-fluorouracil, when the drug achieves therapeutic concentrations throughout the conjunctiva.[27] Possibly a larger probe would further restrict any surrounding fibroblast recruitment.

The use of β radiation has advantages over 5-fluorouracil in that the radiation is relatively localised to the area of treatment. The strontium-90 applicator is portable (even with appropriate shielding and precautions) and can be used an infinite number of times without further cost until the dose rate has decayed so much as to make the length of treatment impracticable. This may be important in certain circumstances and in areas of the world where pharmacological treatment is not practical. It is more convenient to deliver β radiation than to perform multiple subconjunctival injections after surgery. If further studies confirm its efficacy in similar doses to those used clinically at present, the lack of notable side effects may make it suitable for use in primary filtering surgery, not simply in high risk patients but in all patients undergoing filtering surgery. However, as with 5-fluorouracil, the optimum dosage and precise clinical role have not been fully established. Further studies in the laboratory and in the clinical setting are required.

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# Trabeculectomy combined with β irradiation for congenital glaucoma

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## Abstract

**Sixty-six eyes with congenital glaucoma were subjected to trabeculectomy between July 1975 and June 1989 are presented. Thirty-one were treated with β irradiation at the time of surgery with a strontium-90 applicator; 35 were not treated with β irradiation. The usual dose was 750 rad. Analysis was limited to three years because of the shorter follow-up of the irradiated eyes. Failure in the two groups was compared statistically. When failure was categorised as IOP >21 mm Hg, β irradiation was found to be significantly protective with an adjusted risk ratio of 0·31 (95% confidence interval 0·11–0·90, $p<0·05$). Failure categorised as the need for additional medical treatment or further surgery showed significant protection with an adjusted risk ratio of 0·33 (confidence interval 0·12–0·94, $p<0·05$). Multiple regression models were used for the analysis of intraocular pressure; β irradiation was associated with a significantly lower IOP at six months, one year, and three years ($p<0·05$). Other factors identified as being associated with a reduced failure rate or lower IOP were: no previous topical glaucoma medications: age over seven years; lack of previous surgery involving the conjunctiva. The results indicate that β irradiation may have a beneficial effect on the prognosis of trabeculectomy in children with congenital glaucoma. However, because of the retrospective and observational nature of the study, the results must be regarded as tentative.**

Many children with congenital glaucoma respond adequately to one or more surgical procedures of goniotomy or trabeculotomy.[1] A persistent or recurrent rise in intraocular pressure (IOP) may necessitate filtration surgery even though trabeculectomies in children have less satisfactory results than in older patients.[2,3] The results of surgery may also be worse depending on the type of glaucoma and on previous surgery.[2,4] Among the important causes of failure is the cessation of filtration due to fibrous tissue formation in the region of the scleral flap.

In adults adjunct therapy may improve the results of surgery by limiting the wound healing response and reducing the formation of fibrous tissue. Topical steroids significantly improve the results of trabeculectomy in patients with primary open angle glaucoma and primary acute angle glaucoma.[5] 5-Fluorouracil reduces the number of failures in patients with a poor prognosis but is also associated with complications such as corneal epithelial defects[6] and wound leaks.[7,8] In addition the frequent subconjunctival injections make the use of 5-fluouracil impracticable in children.

β Irradiation has been used intermittently in glaucoma fistulising surgery for many years,[9-16] but all reports were of small numbers of patients, and the irradiation tended to be used in mixed groups of patients with poor prognosis. There are no convincing data from these studies to suggest that β irradiation improves control of the IOP, and so the technique has not gained popularity.

Animal studies on the effect of irradiation on the healing of skin wounds[17] showed reduced numbers of fibroblasts and reduced collagen, and the fibroblast activity was delayed. Animal studies on fistulising surgery[10,18] and corneal or scleral wounds[19-21] have also demonstrated reduced fibroblast proliferation and reduced collagen formation, so that the authors speculate that irradiation may benefit fistulising surgery. In addition the bleb survival was extended in rabbits.[18]

In this report the results of 66 trabeculectomies performed in children with congenital glaucoma are presented; 31 of these procedures were accompanied by treatment with β irradiation. In this retrospective analysis we show that a statistically significant improvement in IOP control was achieved in the group treated with β irradiation, and the rate of failure was significantly reduced. The retrospective collection of data from a period of 14 years means that variables other than β irradiation may have been changing. An attempt has been made to incorporate some of these into the analysis, but the study cannot take account of all factors which might influence the results of surgery.

## Materials and methods

All patients aged 18 years or less with congenital glaucoma who were attending Moorfields Eye Hospital under the care of NSCR and had a trabeculectomy between July 1975 and June 1989 were identified. Data were collected from the hospital notes. One eye only from each patient was entered into the analysis.

The surgery in each case was performed by one surgeon (NSCR). Those eyes which had trabeculectomies prior to 1984 did not have β irradiation. There was a short transition period of changing management, but after 1985 all eyes were treated. In those eyes treated with β irradiation a strontium-90 applicator, semicircular in shape and measuring 5·5 mm in radius, was applied immediately after the end of the surgical procedure while the patient was still anaesthetised. It was positioned over the conjunctiva at the operation site with the anterior edge of the applicator at the limbus. The usual dose was 750 rads except for one eye which had 500 rads.

Since the two groups of irradiated or non

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*Table 1 The risk factors which were divided into categories for analysis, and the definition of each of the categories*

| | Group 1 | | | | Group 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | *Definition* | *No β* | *β* | *Total* | *Definition* | *No β* | *β* | *Total* |
| Age at surgery | <7 yr | 15 | 19 | 34 | ≥7 yr | 20 | 12 | 32 |
| Number of previous conjunctival operations | 0 | 27 | 27 | 54 | >0 | 8 | 4 | 12 |
| Number of topical glaucoma medications | 0 | 13 | 17 | 30 | >0 | 22 | 14 | 36 |
| Preoperative IOP | <30 | 7 | 13 | 20 | ≥30 | 28 | 18 | 46 |
| Preoperative corneal diameter | ≤13·5 | 17 | 12 | 29 | >13·5 | 10 | 11 | 21 |
| Preoperative cup/disc ratio | ≤0·8 | 11 | 14 | 25 | >0·8 | 18 | 5 | 23 |
| Preoperative visual acuity | ≤6/36 | 22 | 20 | 42 | >6/36 | 13 | 11 | 24 |
| Number of steroid applications (drops) postoperatively | ≤140 | 23 | 18 | 41 | >140 | 9 | 12 | 21 |

irradiated eyes were not running concurrently, it is important to establish the factors other than β irradiation which might affect the surgery. The available data varied between patients depending on their age. For example, visual acuities were not available in the youngest patients; data on corneal diameters were available only in younger age groups; and visual fields were only available in older patients. In addition many children had advanced glaucoma prior to surgery, some with medial opacities with corresponding low visual acuities and offering poor views of the optic discs. All these factors contributed to a reduction in the overall useful data and meant that the main parameters used to assess the effect of β irradiation were the IOP and time of failure.

The time of failure was defined in two separate ways: (1) The time that the IOP was first above 21 mm Hg, even if subsequent measurements were less than 21 mm Hg. (IOP data were only collected after 3 months.) (2) The time that glaucoma medications were started or further glaucoma surgery was required.

### STATISTICAL ANALYSIS

One eye only for each patient was included in the analysis; if both eyes were operated on at different times, then only the right eye was entered into the study. If an eye had more than one trabeculectomy at Moorfields Eye Hospital, then only the first procedure was entered.

Eyes were grouped into those whose treatment included irradiation and those not so treated. Differences between the groups were analysed with independent sample *t* tests for continuous variables, and $\chi^2$ or Mann-Whitney test for categorical variables.

A correlation matrix was calculated for all variables to identify any large intercorrelations.

Kaplan-Meier survival curves were calculated for the whole study population for each of the failure categories using different variables as the grouping factor. Multivariate survival analysis used Cox's proportional hazards model.[22,23]

The IOP data were analysed by means of a multiple regression model at each time point.[24] Variables were entered into the model by forward, stepwise selection if the 'probability to enter' was less than or equal to 0·05. Additional factors were then forced into the model to test their effect. An explanation of Cox's proportional hazards and multiple regression techniques may be found elsewhere.[22-24]

For the Kaplan-Meier and multiple regression analysis grouped data rather than continuous variables were used. Groupings are shown in Table 1. For both types of model several different models were calculated initially. From these models it was possible to determine those variables which were not significantly affecting the model but which had missing values. A missing value in a variable leads to the exlusion of that eye from the entire analysis. If reasonable, these variables were excluded so that the final model had the maximum number of procedures in it.

The data used for the Cox proportional hazards and multiple regression models were confined to the first three years, because only two of the procedures which were accompanied by β irradiation had a longer follow-up than three years.

## Results

We identified 112 trabeculectomy procedures which were performed during the 14-year period on children with congenital glaucoma aged 18 years or less. The hospital records of six of these patients were not found, and in a further six there was no follow-up because patients were returned to the care of the referring ophthalmologist immediately after surgery. Two patients had peroperative choroidal haemorrhages which were unrelated to the use of β irradiation and were therefore excluded. Of the patients undergoing the remaining 98 procedures 66 (66 eyes) fitted the entry criteria. Only one operation per patient was entered to reduce bias by entering both eyes of the same patient or the same eye twice; if both eyes were operated upon, the right eye was always entered. Most of the eyes had had

*Table 2 The previous surgical procedures. Eyes had up to a maximum of five previous operations prior to the trabeculectomy entered into the study*

| *Operation.* | *1st* | *2nd* | *3rd* | *4th* | *5th* | *Total* |
|---|---|---|---|---|---|---|
| *No β irradiation at time of surgery* | | | | | | |
| Goniotomy | 23 | 10 | 3 | 1 | 1 | 38 |
| Trabeculotomy* | 3 | 1 | | | | 4 |
| Trabeculectomy* | 2 | 1 | | | | 3 |
| Scheie* | 1 | | | | | 1 |
| Cyclocryotherapy | 2 | | | | | 2 |
| Cycloanaemation* | 1 | 1 | | | | 2 |
| Other | 1 | 1 | | | | 2 |
| *With β irradiation at time of surgery* | | | | | | |
| Goniotomy | 23 | 11 | 1 | | | 35 |
| Trabeculotomy* | 1 | 2 | 1 | | | 4 |
| Trabeculectomy* | | | | | | 0 |
| Scheie* | | | | | | 0 |
| Cyclocryotherapy | | | | | | 0 |
| Cycloanaemation* | | | | | | 0 |
| Other | 2 | 2 | 1 | | | 5 |

*Procedures which were included in the category of 'previous procedures involving the conjunctiva'

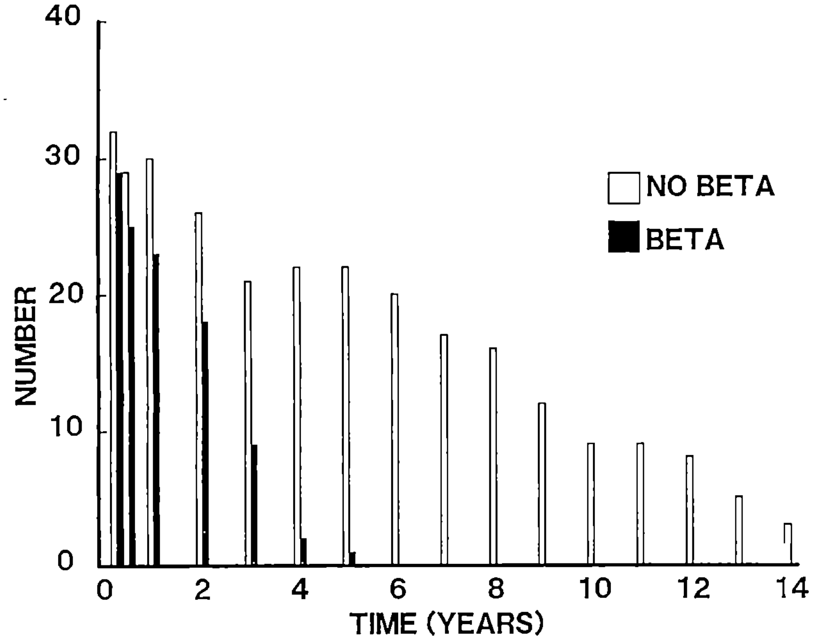

*Figure 1 Graph showing the number of eyes (patients) with data available for analysis at each time point. Data was collected at 3 months, 6 months, one year and every year thereafter.*

previous surgery at Moorfields Eye Hospital or the referring hospital, and some eyes had had previous surgery affecting the conjunctiva (Table 2). Only the first trabeculectomy performed at Moorfields Eye Hospital was entered.

Three patients (three procedures) were removed at a later date. Two patients had an ocular injury which ultimately led to the loss of all vision, and one patient died. These patients were not treated as failures but as if they had been lost to follow-up at the time of the injury/death.

*Table 3 Comparison of the preoperative risk factors in the β irradiated and non-β -irradiated eyes by the t test. No=number of eyes with available data*

| | *No β* | | | *β* | | | |
|---|---|---|---|---|---|---|---|
| | *No* | *Mean* | *SD* | *No* | *Mean* | *SD* | *p* |
| Age at diagnosis if glaucoma | 34 | 1·8 | 2 6 | 29 | 1·1 | 2·2 | 0 27 |
| Age at trabeculectomy | 35 | 7·7 | 4·0 | 31 | 5·1 | 4·2 | 0·011 |
| No of previous operations | 35 | 1 5 | 0 9 | 31 | 1·4 | 0·9 | 0·868 |
| No of previous operations of conjunctiva | 35 | 0·29 | 0 6 | 31 | ·13 | 0·3 | 0 189 |
| No of previous glaucoma drop applications | 35 | 1162 | 2832 | 31 | 303 | 760 | 0 16* |
| No of different previous glaucoma medications | 35 | 0·83 | 0·7 | 31 | 0·55 | 0·7 | 0 117 |
| Preoperative IOP | 35 | 33·6 | 6·7 | 31 | 28·8 | 5·6 | 0 003 |
| Preoperative cup/disc ratio | 29 | 0·9 | 0·2 | 19 | 0·79 | 0·1 | 0 043 |
| Preoperative corneal diameter | 27 | 13·4 | 1·0 | 23 | 14·0 | 1·0 | 0·035 |

* Mann-Whitney test. Mean=mean for each eye.

*Table 4 Comparison of the preoperative risk factors in the β irradiated and non-β-irradiated eyes by $\chi^2$ analysis. Number/total indicates the number in that subgroup and the total of all eyes with available information for that particular subgroup*

| | *No β* | | *β* | | |
|---|---|---|---|---|---|
| | *Number total* | *%* | *Number total* | *%* | *p* |
| Caucasian | 34/35 | 97·1 | 30/30 | 100 | 1·00 |
| Male | 19/35 | 54·3 | 21/31 | 67·7 | 0·40 |
| Right eye | 27/35 | 77·1 | 19/31 | 61·3 | 0·26 |
| Isolated trabecular dysgenesis | 22/35 | 62 9 | 22/31 | 70 | 0 66 |
| Iridocorneal dysgenesis | 5/35 | 14·3 | 0/31 | 0 | 0·08 |
| Aniridia | 1/35 | 2·9 | 1/31 | 3·2 | 1·00 |
| Sturge-Weber | 2/35 | 5 7 | 6/31 | 19·4 | 0·19 |
| Neuro-fibromatosis | 5/35 | 14·3 | 1/31 | 3·2 | 0 26 |
| Visual acuity | 28/35 | | 17/31 | | 0 31* |

* Mann-Whitney test

*Table 5 Comparison of the preoperative risk factors in the β irradiated and non-β-irradiated eyes by $\chi^2$ analysis. The table structure is similar to that of Table 4. Conjunctival flaps were either limbal or fornix based*

| | *No β* | | *β* | | |
|---|---|---|---|---|---|
| | *Number total* | *%* | *Number total* | *%* | *p* |
| New site for surgery | 35/35 | 100 | 31/31 | 100 | NA |
| Sutures to scleral flap | 33/34 | 97 1 | 31/31 | 100 | 1·0 |
| Vitreous loss | 1/35 | 2·9 | 0/31 | 0 | 1·0 |
| Fornix based conj flap | 14/30 | 46·7 | 31/31 | 100 | 0·000 |

The 66 eyes used in the analysis had surgery over a period of 14 years with variable length of follow-up (Fig 1). Those which had trabeculectomies prior to 1984 did not have β irradiation. There was a short transition period of changing management, but after 1985 all eyes were treated. *T* Test and $\chi^2$ calculations for pre-, per-, and postoperative factors are given in Tables 3 to 6 and show several significant differences between the two groups.

Part of the correlation matrix is shown in Table 7 and identifies all pairs of factors which have a significant correlation.

The differences between the groups treated or not treated with β irradiation and the correlating variables all occur in potential risk factors, so the statistical analysis needs to control for these confounding variables.

The graphs for the Kaplan-Meier estimation for the two categories of failure with β irradiation used as the stratification factor are shown in Figs 2 and 3. These graphs suggest separation of the groups, but they do not take into account other factors which might affect the success or failure. To examine the effects of other risk factors and the interaction of these factors a Cox proportional hazards model was established for each of the two failure categories.

In the Cox proportional hazards models the preoperative visual acuity, cup-disc ratio, corneal diameter, type of conjunctival flap, and postoperative steroid regimen were found to reduce markedly the numbers available for analysis because of missing values for different eyes. Preoperative visual acuity data were available only for older children, and since inclusion would confine the analysis to that group only it was excluded. Preoperative cup-disc ratios and postoperative steroid regimens were categorised to form approximately equal groups. The groups so formed had doubtful clinical relevance, and since they were found to have no particular effect on the models in the initial analyses they were excluded.

The type of conjunctival flap (limbal or fornix based) had marked collinearity with irradiation treatment and was thought to be an important risk factor which should be kept in the models to ensure that the improved results associated with irradiation were not in fact due to the type of conjunctival flap.[25] In the Cox proportional hazards models the type of conjunctival flap was

*Table 6 Comparison of the postoperative risk factors in the β irradiated and non-β -irradiated eyes by* t *test analysis. The table structure is similar to that of Table 3*

| | *No β* | | | *β* | | | |
|---|---|---|---|---|---|---|---|
| | No | Mean | SD | No | Mean | SD | p |
| Total number of postoperative steroid drops | 32 | 34 | 15·3 | 30 | 35 | 10·3 | ·692 |

*Table 7 Part of correlation table showing all the significant correlations between paired risk factors. No other risk factors were found to correlate significantly*

| | *Treatment with β irradiation* | *Age <7 years* | *Age of diagnosis* | *Corneal diam. >13·5 mm* | *Previous conjunctival surgery* |
|---|---|---|---|---|---|
| Previous topical treatment | | 0·40** | | | |
| Preop. IOP >30 mm Hg | | 0·44** | | | |
| Limbal based conjunctival flap | −0·61* | | | | |
| Postop. steroid >140 drops | | 0·36** | | | −0·35* |
| Preop. cup/disc >0·8 | −0·35* | | | | |
| Previous surgery | | | −0·33* | 0 43* | |

*p<0·01 **p<0 001 Pairwise calculations.

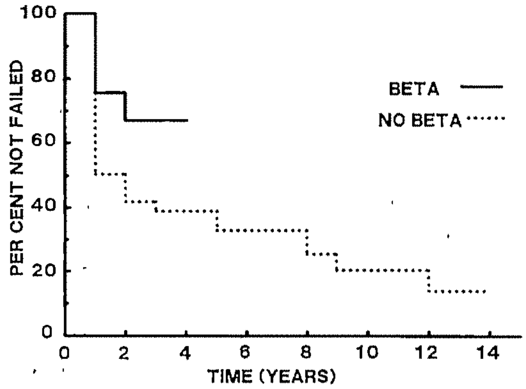

*Figure 2 Kaplan-Meier survival curve. Failure is categorised as the time at which the IOP was first above 21 mm Hg.*

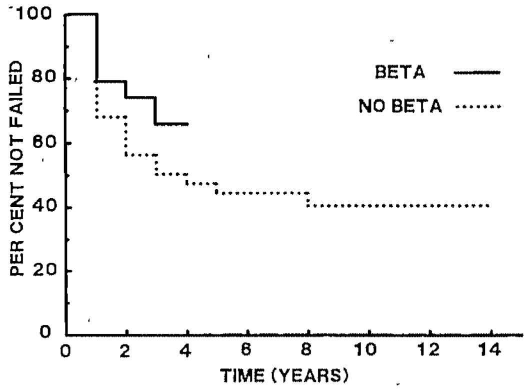

*Figure 3 Kaplan-Meier survival curve. Failure is categorised as the time at which further medical or surgical treatment was required to control the IOP.*

the last factor to enter each model. It was not a significant factor, but it did influence the p values of the other factors already in the model. It was therefore considered necessary to include this risk factor, though the eyes available for analysis were reduced from 66 to 61 because of missing values. The final Cox proportional hazards models for the two failure categories are shown in Tables 8 and 9.

The difference in IOP with only β irradiation used as the stratification factor is shown in Fig 4. The multiple regression models which include significant factors only are summarised in Table 10. These significant factors were identified by the forward, stepwise selection if the probability to enter was less than or equal to 0·05. The models suggest that treatment with β irradiation has a highly significant effect in improving the quality of IOP control at all time points except three months. However, these models do not take account of the other factors which affect the IOP, even if these other factors are not significant themselves. Therefore the same risk factors that were used in the Cox proportional hazards models were forced stepwise in order of significance until all factors were entered into the model.

The significance of treatment with β irradiation was reduced at each time point in these new models, but remained significant ($p<0{\cdot}05$) except at two years. The new models are summarised in Table 11. In these models the effect of preoperative medical treatment maintained its original pattern of significance at three and six months and one year, though the significance was reduced from its previous levels. The significance of the type of conjunctival flap and effect of previous conjunctival surgery was lost ($p>0{\cdot}05$) in the new model. Table 11 shows the order in which the variables entered the models and the p value of each. Multiple regression does not provide information in any absolute terms about the relative importance of independent variables (that is, hazard ratios), so further details are not included.

The main postoperative complications were related to the increase in IOP and the need for further treatment. A list of other early and late complications is given in Table 12.

## Discussion

This analysis suggests that treatment of the trabeculectomy site with β irradiation at the time of surgery has a beneficial effect in children with congenital glaucoma. Failure categorised by a rise in IOP above 21 mm Hg showed that β irradiation was significantly protective with an adjusted risk ratio of 0·31 (95% confidence interval 0·11–0·90, $p<0{\cdot}05$). Failure categorised as the need for additional medical treatment or further surgery showed significant protection with an adjusted risk ratio of 0·33 (confidence interval 0·12–0·94, $p<0{\cdot}05$).

Irradiation was associated with a significantly improved quality of IOP control at six months, one year, and three years ($p<0{\cdot}05$). It was not significant at three months or two years. These IOP results included eyes on additional glaucoma treatment, which was greater amongst the non-irradiated eyes, but excluded eyes which had undergone further surgery.

Apart from β irradiation, another strong factor determining the outcome of surgery was the use of topical medications prior to surgery. This was a significant factor which increased the incidence of failure in both of the failure categories. Failure categorised by a rise in IOP above 21 mm Hg showed an adjusted risk ratio of 5·56 (95% confidence interval 1·77–17·44, $p<0{\cdot}01$), and failure categorised by medical treatment or further surgery showed an adjusted risk ratio of 7·24 (confidence interval 2·01–26·07, $p<0{\cdot}01$). The use of preoperative topical glaucoma medications reduced the quality of IOP control at three months, six months, and one year ($p<0{\cdot}05$). This supports the findings of recent

*Table 8 Cox proportional hazards model with each of the listed factors forced into the model. The hazard ratio for each factor takes into account the effect of each of the factors and adjusts for confounding variables*

| | *Coefficient* | *SE* | *p Value* | *Hazard ratio* | *95% confidence limits* | |
|---|---|---|---|---|---|---|
| Treatment with irradiation | −1 16 | (0·54) | 0·031 | 0·31 | 0·11 | 0·90 |
| Previous topical treatment | 1 71 | (0·58) | 0 003 | 5·56 | 1·77 | 17·44 |
| Previous conjunctival surgery | −1 36 | (0 70) | 0 052 | 0·26 | 0 06 | 1·01 |
| Age >7 years at surgery | −1 13 | (0·53) | 0 034 | 0·32 | 0·11 | 0·92 |
| Isolated trabecular dysgenesis | 0 24 | (0 46) | 0·60 | 1·28 | 0 52 | 3·15 |
| Female | −0·31 | (0·47) | 0·501 | 0·73 | 0 29 | 1·83 |
| Limbal based conj flap | 0·19 | (0·50) | 0·702 | 1·21 | 0·45 | 3·24 |
| Preop IOP >30 mm Hg | −0 12 | (0·56) | 0·836 | 1·12 | 0·37 | 3·39 |
| | Deviance = | | 187 48 | | | |
| Likelihood ratio statistic on | 8 DF = | | 22 39, p=0 004 | | | |
| | Number=61 | | | | | |

*Table 9 Cox proportional hazards model for failure=further surgery or medical treatment*

| | *Coefficient* | *SE* | *p Value* | *Hazard ratio* | *95% confidence limits* | |
|---|---|---|---|---|---|---|
| Previous topical treatment | 1 98 | (0·65) | 0·002 | 7·24 | 2·01 | 26·07 |
| Previous conjunctival surgery | −1 5 | (0 72) | 0 038 | 0·22 | 0·05 | 0 92 |
| Age >7 years at surgery | −1·64 | (0 63) | 0 009 | 0 19 | 0 06 | 0·66 |
| Treatment with irradiation | 1 1 | (0·53) | 0·038 | 0·33 | 0·12 | 0·94 |
| Preop IOP >30 mm Hg | 0 81 | (0·6) | 0·175 | 2·24 | 0·7 | 7·21 |
| Female | −0·73 | (0 5) | 0·151 | 0 48 | 0 18 | 1·3 |
| Isolated trabecular dysgenesis | 0 71 | (0·48) | 0·137 | 2 03 | 0·8 | 5·16 |
| Limbal based conj flap | −0·63 | (0·54) | 0·250 | 0·53 | 0·18 | 1·55 |
| | Deviance = | | 158·87 | | | |
| Likelihood ratio statistic on | 8 DF = | | 21·02, p=0 007 | | | |
| | Number=61 | | | | | |

*Table 10 Multiple regression model of factors influencing the postoperative IOP. The model contains only those factors which were significant. The effect of other risk factors is not included, which inappropriately exaggerates the beneficial effect of β irradiation, as shown by the high p values in this table compared with Table 11*

| *IOP at* | *3 mth* | *6 mth* | *1 yr* | *2 yr* | *3 yr* |
|---|---|---|---|---|---|
| Treatment with β irradiation | | <0·001 | <0·005 | <0·01 | <0·05 |
| Previous topical glaucoma treatment | <0·05 | <0·005 | <0 05 | | |
| Limbal based conj flap | <0 01 | | | | |
| Previous conjunctival surgery | | | | | <0·05 |

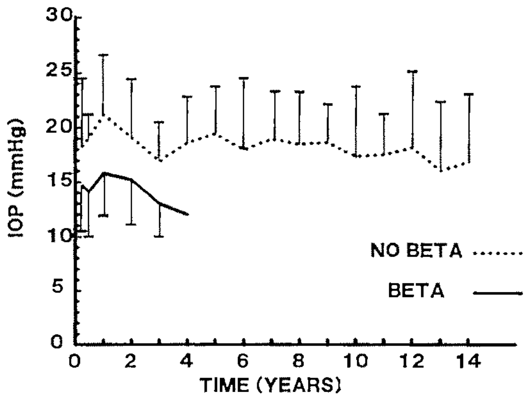

*Figure 4 The mean postoperative IOP of eyes treated or not treated with β irradiation. The first postoperative IOP is at three months.*

studies in adults which suggest that early surgery (as opposed to surgery following failure of medical treatment) may improve the final surgical outcome.[23 26]

Another significant factor in the Cox proportional hazards models was the age at surgery. Children older than 7 years had a lower hazard ratio than patients less than 7. For failure categorised as IOP >21 mm Hg the adjusted risk ratio=0·32 (95% confidence interval 0·11–0·92, p<0·05). For failure categorised as further medical treatment or surgery the adjusted risk ratio=0·19 (95% confidence interval 0·06–0·66, p<0·05). This supports the findings of previous publications that younger patients do not do so well as older.[2]

Previous surgery involving the conjunctiva also significantly increased the risk of failure in the model of failure categorised as the need for further surgery or medical treatment, adjusted risk ratio=0·22 (95% confidence interval 0·05–0·92, p<0·05).

The study suffers from a number of problems which affect retrospective studies. In particular several of the pre- and peroperative risk factors in the patients treated and not treated with β irradiation were not equal, and the analysis was complicated by multicollinearity. The correlations reflect a change in management of these patients over 14 years. β Irradiation was used in the later years only; surgery began to be used at an earlier stage rather than medical treatment; children were operated upon with trabeculectomy at a younger age; and the type of conjunctival flap changed from limbal based to fornix based. All these variables affect the hazard ratios, and yet they significantly correlate with each other. It is because of these correlations and interactions that the analysis requires such complex models to be calculated which control for confounding variables.

The most important of the identified correlating risk factors was the association between treatment with β irradiation and the type of conjunctival flap (limbal or fornix based). However, β irradiation was repeatedly the more significant factor in the models, and the type of conjunctival flap was not shown to have a significant effect in either of the categories of failure. It entered the multiple regression models after β irradiation (except at three months) and was not significant at any time point.

In addition to these identifiable factors there may have been other unidentified and unmeasurable factors affecting the patient selection, surgery, or postoperative management. The retrospective collection of the data means that the models cannot adequately control for all confounding variables, and despite the complex statistical analysis it is not possible to be certain that β irradiation is an important factor as opposed to some other unmeasured confounding variable. Therefore the conclusion that β irradiation improves the prognosis for trabeculectomy in children with congenital glaucoma must be regarded as tentative.

### DOSE OF β IRRADIATION

The dose of β irradiation used in each case was 750 rads except in one of the early cases, which had 500 rads. The results in this report demonstrate that 750 rads has a significant effect without an increased incidence of complications, but the ideal dose is not known. Higher doses have been reported to cause a variety of side effects, including ocular irritation immediately following treatment, delayed or persistent

*Table 11 Multiple regression model of factors influencing the postoperative IOP, with each of the listed risk factors forced into the model. The level of significance shown in Table 9 has been reduced with the inclusion of other risk factors which are also influencing the results, though they are not themselves significant*

| | *3 Months* | | | *6 Months* | | | *1 Year* | | | *2 Years* | | | *3 Years* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Ord* | *B* | *p* | *Ord* | *B* | *p* | *Ord* | *B* | *p* | *Ord* | *B* | *p* | *Ord* | *B* | *p* |
| Treatment with irradiation | 5 | −2·0 | 0·26 | *1* | *−3·5* | *0·012* | *1* | *−4·3* | *0·04* | 1 | −4·3 | 0·06 | *1* | *−5·2* | *0·02* |
| Previous topical treatment | 2 | 3·5 | 0·04 | *2* | *3·0* | *0·02* | *2* | *−4·1* | *0·04* | 2 | 4·5 | 0·14 | 8 | −1·2 | 0·65 |
| Limbal based conj. flap | 1 | 2·6 | 0·21 | 8 | 1·9 | 0·89 | 4 | 2·0 | 0·37 | 7 | 0·6 | 0·79 | 7 | −1·5 | 0·46 |
| Isolated trabecular dysgenesis | 3 | 2·4 | 0·12 | 4 | 0·9 | 0·42 | 8 | 1·8 | 0·69 | 3 | −3·0 | 0·17 | 4 | −2·7 | 0·25 |
| Female | 4 | −1·2 | 0·4 | 5 | −0·4 | 0·73 | 5 | −1·8 | 0·30 | 8 | 0·4 | 0·82 | 6 | 2·3 | 0·30 |
| Previous conj surgery | 6 | −2·4 | 0·23 | 3 | −1·7 | 0·24 | 3 | −2·3 | 0·33 | 4 | −1·7 | 0·58 | 2 | −4·8 | 0·09 |
| Preop IOP >30 mm Hg | 8 | −0·8 | 0·63 | 6 | −0·6 | 0·63 | 7 | 1·8 | 0·36 | 6 | 0·8 | 0·73 | 3 | 0·0 | 0·99 |
| Age >7 years at trabeculectomy | 7 | −1·6 | 0·35 | 7 | 0·6 | 0·63 | 6 | −2·0 | 0·34 | 5 | −1·4 | 0·64 | 5 | 3·5 | 0·24 |

Ord=order of entry into the model. B=partial regression coefficient. Those p values in italic are <0·05

*Table 12 Summary of the postoperative complications in the eyes which were or were not treated with β irradiation*

| | *No Irradiation Number=35* | *β Irradiation Number=31* |
|---|---|---|
| *Early complications* | | |
| Shallow anterior chamber | 18 (51·4%) | 10 (32·3%) |
| Hyphaema | 13 (37·1%) | 10 (32·3%) |
| Low IOP | 8 (22·9%) | 6 (19·4%) |
| Choroidal detachment | 3 (8·6%) | 3 (9·6%) |
| *Late complications* | | |
| Cystic bleb | – | 5 (16%) |
| Cataract surgery | 1 (2·9%) | 1 (3·2%) |
| Corneal decompensation | 1 (2·9%) | – |
| Keratoplasty (iridocorneal dysgenesis) | 1 (2·9%) | – |
| Retinal detachment | 1 (2·9%) | 1 (3·2%) |
| Corneal abscess | 1 (2·9%) | – |
| Endophthalmitis | – | 1 (3·2%) |
| Band keratopathy | 2 (5·7%) | – |

irritation, telangiectasis causing haemorrhage, ischaemic areas, loss of lashes, late corneal ulceration and 'epidermalisation' of the conjunctiva.[27] Cataracts may form with high doses.[27-31] Cataracts have been estimated to occur at doses above 2000 to 4000[29] and 3000 rep to be a non-cataractous dose when used in the treatment of pterygia.[30] Cataracts were identified in 38% of 71 patients followed up for 5–21 years with doses of 6460–90 000 rads,[31] but lens opacities have also been recorded at lower doses and were identified in 19% of 83 eyes at 4–8 years with 1800–2200 rads for pterygia.[32] Doses of 20 000 rads have also caused telangiectasis, lipid infiltration of the cornea, and corneal thinning.[31] All these doses are higher than the 750 rads used in the majority of patients in this report.

In animal studies in rabbits doses of 2500 rads produce an increased survival time of the blebs, but the blebs are extremely thin.[18] The thin blebs may be undesirable and suggest that 2500 rads may be too high in man.

In the children treated with β irradiation in this report no children developed cataracts which were thought to be associated with the irradiation, and they did not develop irritable eyes or telangiectasia. A list of complications in both treated and untreated groups is given in Table 12. The retrospective collection of these data means that some of it is unreliable, particularly the early postoperative complications. Despite these reservations it is interesting to note that the recorded incidence of early complications is similar in each group.

The late complications of corneal decompensation (one leading to a corneal abscess), band keratopathy, retinal detachments, and the need for corneal or cataract surgery reflect the poor health of these eyes rather than the consequences of trabeculectomy or β irradiation. There is no suggestion that treatment with β irradiation causes or worsens these problems.

The increased incidence of cystic blebs in the irradiated eyes is an important observation. The apparent incidence of 16% of eyes developing cystic blebs following β irradiation is not the clinical impression. The category of cystic bleb can cover a wide spectrum from minor to grossly cystic with extreme thinning. Eyes treated with 750 rads of β irradiation tends to develop blebs which are not cystic, are slightly elevated, and are not inflamed. If the bleb wall does become thin or cystic, then it is of minor degree only with 750 rads in children. There were no cases of perforated blebs or persistent wound leak in eyes treated with irradiation. We believe that the retrospective collection of these observations has provided unreliable data which do not reflect the true situation. The eyes which were not treated with β irradiation were treated at a time when it was still common to see the cystic blebs that followed the Scheie procedure. An eye which might be defined today as cystic may not have been considered to be cystic in the post-Scheie era.

### TIMING OF IRRADIATION

To our knowledge no studies have been performed which consider the ideal time to apply the irradiation to the trabeculectomy site. The options are: prior to surgery; at the time of surgery; some time after surgery; and in fractionated doses. In experimental skin wounds in rats[17 33-35] 1000 r given 1 to 30 days before the incision, incision had no perceptible effect on wound healing, but immediately, 24 hours, and 48 hours after incision radiation retarded healing, though at no time did it affect the final scar. The most marked delay was observed with treatment at 24 hours. The difference in effect depends on the stage of mitosis of the cell.[36] The cell is most sensitive to irradiation during mitosis itself. It is relatively resistant during the $G_1$ phase, but radiosensitivity returns during the late $G_1$ and early synthetic phase (S) and early $G_2$ phases. The greatest effect in skin wounds at 24 hours reflects the activity of transcription and mitosis of the fibroblasts at this time. It is interesting to note how rapidly the state of the fibroblasts must change following surgical injury because radiotherapy one day prior to incision does not influence the repair, and yet treatment immediately after incision does have an effect.

In fistulising surgery, particularly in children,

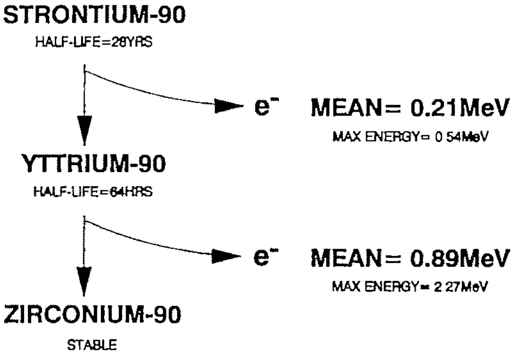

*Figure 5 Decay path of strontium-90 showing emission and energy of β particles which are electrons of negligible mass and one negative charge, and therefore rapidly slowed down when passing through tissues*

the application of the radiation source is very convenient immediately after surgery. The operating theatre is a restricted area and therefore handling radioactive sources in the theatres is simplified. The child is already anaesthetised, and the operative procedure is extended by less than five minutes. Treatment at 24 to 48 hours or in fractionated doses would require further sedation in children.

An important consideration during treatment is the effect of a raised, aqueous filled bleb at the site of application. Strontium-90 emits β particles which are electrons of negligible mass, one negative charge, and therefore rapidly slowed down when passing through tissues. Strontium-90 decays to yttrium-90 which decays to zirconium-90, which is stable.[32] The β rays of yttrium-90 have the greatest energy, with a mean of 0·89 MeV (Fig 5). Electrons of 2 MeV have a maximum range of about 1 cm of water, with a rapid fall off in penetration below the surface. Application of the β source to a raised bleb will give maximal treatment to the elevated conjunctiva, less to the fluid filled contents of an elevated bleb, and still less to the episclera and sclera. Since the episclera is an important source of fibroblasts following fistulising surgery, it is undesirable to place an additional barrier (the fluid filled bleb) between the β source and the tissue. It follows that a more satisfactory and consistent dose (and the most convenient) will be achieved immediately after the end of the surgical procedure when the patient is asleep and the bleb has not yet formed.

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**REFERENCES:** 1. Jones FL, Ekberg NL: letter N Eng J Med 1979; **301**: 270.
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# Heterogeneity in dominant anterior segment malformations

Gerd E Holmström, William P Reardon, Michael Baraitser, John S Elston, David S Taylor

## Abstract

**Peters' anomaly is usually a sporadic or autosomal recessive condition. We present three families whose members had dominantly inherited anterior segment anomalies with variable expression, including typical Peters' anomaly in at least one family member. Slit-lamp examination of parents and family members of children with Peters' anomaly is therefore important to exclude dominant inheritance.**

A variety of anomalies may be seen as a result of disturbances of the development of the anterior segment of the eye, including Peters' anomaly, Rieger's anomaly, Axenfeld's anomaly, and sclerocornea. Many individual cases fit into the more clearly defined patterns or syndromes but they often overlap, defying specific description.

Peters' anomaly consists of a central corneal leucoma, a central defect of Descemet's membrane, and synechiae between the iris and the cornea.[1] The affected cornea is rarely vascularised, and the peripheral cornea is clear, though scleralisation of the limbus is common.[2] Keratolenticular adherence with shallowing of the anterior chamber may be seen.[2 3] 80% of the cases are bilateral and glaucoma may occur in 50% of the cases.[4] Other associated findings include congenital cataract, which may be related to the corneal opacity, microphthalmos, coloboma, cornea plana, sclerocornea, and dysgenesis of the angle and the iris.[3–5] Congenital perforation of the cornea has also been reported.[6 7] Associated systemic findings affecting the central nervous system, cardiovascular system, urogenital system, digestive system, skull and face, and limbs are reported.[4] Histologically the posterior cornea shows the most significant changes. The periphery is normal, but the central part shows an absence or marked attenuation of the endothelium and Descemet's membrane.[2 3] Changes in the angle, in the form of numerous iris processes adherent to the trabecular meshwork, have also been mentioned.[8]

Sclerocornea was first described as an isolated congenital anomaly in 1933.[9] It often occurs together with cornea plana or other ocular anomalies, including microphthalmos, anomalies of the anterior chamber, glaucoma, and coloboma.[2 10 11] In 90% of the cases sclerocornea is bilateral.[2] It may affect either the peripheral or the entire cornea,[12] which assumes an opaque appearance approaching that of the sclera. Macroscopically the opacity usually extends through the full thickness of the cornea.[11] The cornea is vascularised superficially, but the process may extend deeply.[12] Histopathologically the lamellar organisation of the corneal stroma is lost, and similarities to scleral tissues with irregularly arranged collagen fibrils of variable dimensions are seen instead.[10 12–14] Elastic fibres have been described in the anterior stroma.[12 13] The corneal endothelium and the Descemet's membrane are attenuated, incomplete, or absent.[10 12–14]

A prominent Scwalbe's line, sometimes called posterior embryotoxon, has been reported in 8–32% of otherwise normal eyes.[4 15 16] However, Axenfeld[17] used the term 'embryotoxon corneae posterius' when he described a patient with a whitish, prominent line in the posterior periphery of the cornea, close to the limbus, and with iris strands up to this line. Subsequently a prominent Schwalbe line in combination with iris strands to the line has been called Axenfeld's anomaly. It is associated with glaucoma in 50%,[18] this condition being known as Axenfeld's syndrome.

In 1935 Rieger described cases with iris changes including hypoplasia, corectopia, and hole formation, in addition to findings consistent with Axenfeld's anomaly.[19] Subsequently this combination has been known as Rieger's anomaly. In 1969 Alkemade[4] reviewed the literature together with a study of patients with 'dysgenesis mesodermalis of the iris and the cornea'. A detailed description of Rieger's anomaly was given, the main constituents being hypoplasia of the iris stroma and abnormalities of the iridocorneal angle – that is, a prominent Schwalbe's line with iris strands extending over the angle to the Schwalbe ring. Glaucoma occurs in 60% of cases,[4] and an ill defined iridocorneal junction is commonly seen.[4] The cornea is often normal, but microcornea or macrocornea may be seen.[4] Peripheral opacities of the cornea at the site of the irideocorneal adhesions are described,[4] as are central leucomas.[4 20 21] Cornea guttata has also been mentioned.[22] Pupil abnormalities are frequent (72%); abnormalities in shape, size, and location are seen as well as polycoria.[4] Ectropion uveae is described[22] and so are coloboma of the iris[22 23] and lens abnormalities. Epicapsular stars on the anterior lens surface,[4 22 24] colobomas,[4 22] subluxation,[4 20 25] cataracts of many types,[4 20 22] and posterior lens opacities associated with anterior persistent hyperplastic primary vitreous.[26] Rarely other ocular anomalies may be associated: disc anomalies, chorioretinal colobomas, macular degeneration, choroidal hypoplasia, and retinal detachment.[4]

Some patients with Rieger's anomaly have associated non-ocular developmental defects, particularly of the teeth and facial bones.[27 28] The combination of Rieger's anomaly and dental anomalies is called Rieger's syndrome. Many authors fail to distinguish between Rieger's anomaly and Rieger's syndrome. Even the

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original description by Rieger[19] included at least one case which can be identified as Rieger's syndrome by having teeth abnormalities. However, the term 'Axenfeld-Rieger syndrome' has been proposed, since dental defects also have been noted among patients with findings consistent with Axenfeld's anomaly.[29]

Furthermore, it has been suggested that Axenfeld's and Rieger's syndromes may be different expressions of the same gene.[30,31] The dental defects include microdontia, hypodontia, and oligodontia or anodontia.[27,32] Facial abnormalities are a frequent finding, and Rieger described maxillary hypoplasia with flattening of the midface and a short philtrum.[19] A broad, flat nasal root, hypertelorism, and telecanthus have also been described.[4] Many other systemic abnormalities have been reported[4,31]: hand and feet malformations,[4,33,34] cardiovascular anomalies,[4,35] deafness,[4,34] mental deficiency,[4] myopathy,[25,36] skin changes,[4,37] umbilical hernias, and hypospadias.[24,34]

The genetics of this group of conditions as a whole is problematic. It has been suggested by Kivlin *et al*,[38] who report on several patients with Peters' anomaly in one eye and Axenfeld's anomaly in the other eye, that the various components might represent variable expression of mesodermal dysgenesis. However, these authors do not describe the inheritance of these patients. A variable expressivity of a dominant gene in anterior segment anomalies is reported by Hittner *et al*,[39] Salmon *et al*,[40] and Green and Johnson.[41] In the study of Hittner *et al*[39] all family members had cataracts and corneal opacities, but with large phenotypic variation. In the study of Salmon *et al*[40] most affected members had microcornea with cataract but one had a typical Peters' anomaly. In Green and Johnson's study[41] one patient had Peters' anomaly, others had peripheral scleralisation of the cornea, while most patients had microcornea and cataract.

We report on three families which support the contention that Peters' anomaly, Rieger's anomaly, sclerocornea, and Rieger's syndrome might occasionally be the result of variable expression of the same genetic disorder.

## Case reports

*Family 1*

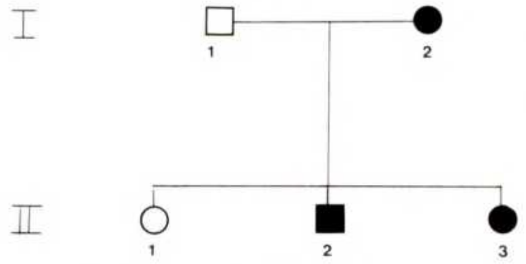

*Figure 1 Pedigree data of family 1. I and II refer to the different generations in the pedigree. 1, 2, 3, etc refer to the individuals within a particular generation. ■=affected male. □=unaffected male. ●=affected female. ○=unaffected female.*

*I 2*

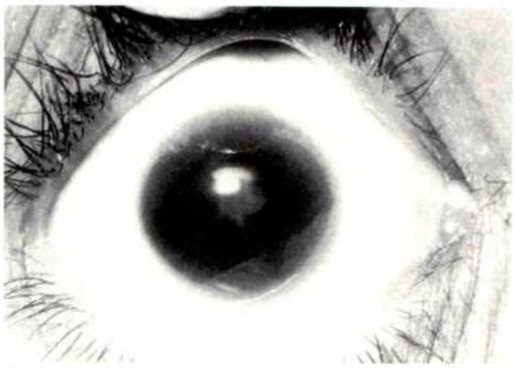

*Figure 2 Case I 2. The right eye of the mother has a microcornea, superior and inferior scleralisation, and a cataract. The visual acuity is counting fingers.*

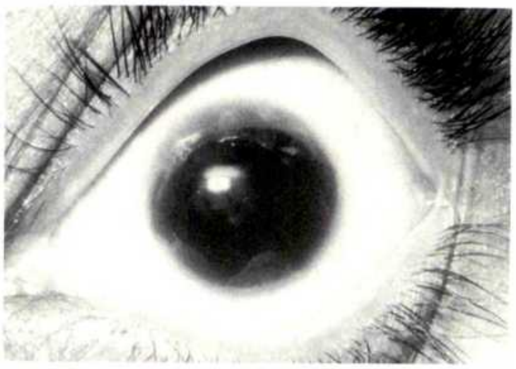

*Figure 3 Case I 2. The left eye has a microcornea, superior scleralisation, and aphakia. The vision is 6/36 with glasses (+13·0).*

*II 2*

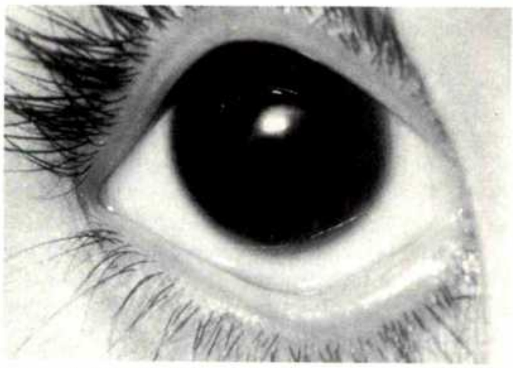

*Figure 4 Case II 2. The right eye of this 5-year-old boy has microphthalmos, slight superior and inferior scleralisation, and peripheral iridocorneal adhesions. There is a horizontal nystagmus, and the best visual acuity is 6/36.*

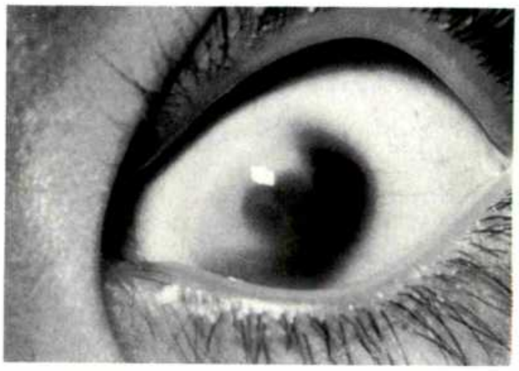

*Figure 5 Case II 2. The left eye has microphthalmos, sclerocornea, and peripheral iridocorneal adhesions and can only localise light.*

*III 3*

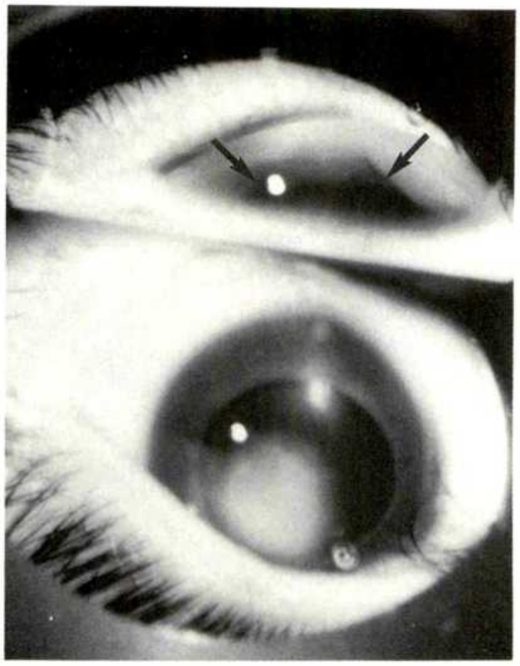

*Figure 6 Case III 3. The right eye of this baby has Peters' anomaly with a central corneal opacity and lens adhesions to the corneal endothelium seen with gonioscope at 3 months of age. The arrows indicate the border of the lens.*

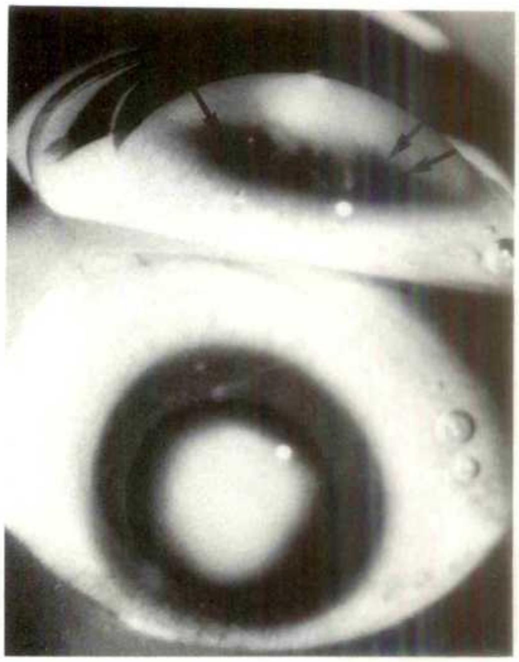

*Figure 7 Case III 3. The left eye has Peters' anomaly with a more pronounced corneal opacity and lens adhesions to the cornea seen at gonoscopy. The arrows indicate the border of the lens.*

*Family 2*

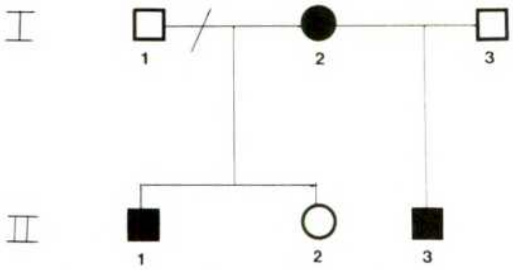

*Figure 8 Pedigree data of family 2.*

*I 2*

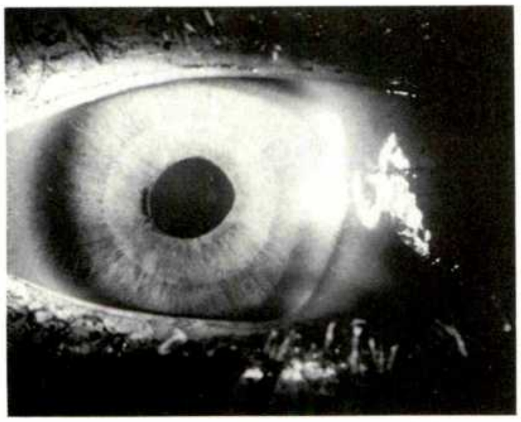

*Figure 9 Case I 2. The right eye has iris hypoplasia, posterior embryotoxon, peripheral iridocorneal adhesions, and a visual acuity of 6/9.*

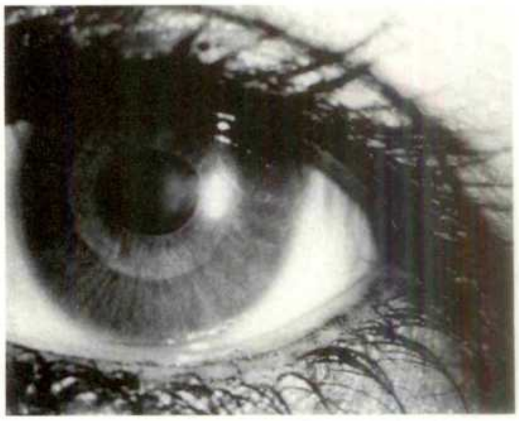

*Figure 10 Case I 2. The left eye also has iris hypoplasia, posterior embryotoxon, peripheral iridocorneal adhesions, and a visual acuity of 6/12 (−2·5 dioptres).*

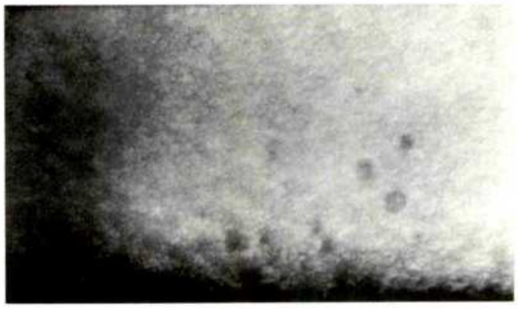

*Figure 11 Case I 2. Enlarged, irregular corneal endothelial cells with focal defects.*

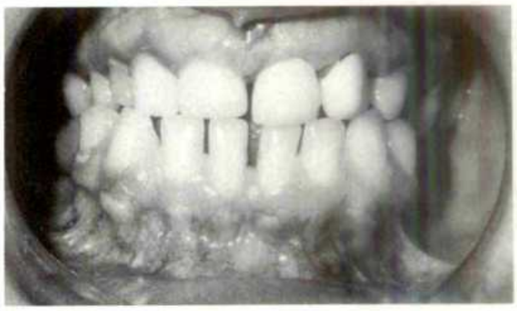

*Figure 12 Case I 2. The mother has short clinical crowns of the two frontal teeth, which have been capped, aplasia of the lateral incisors, and a right side cross-bite.*

II 1

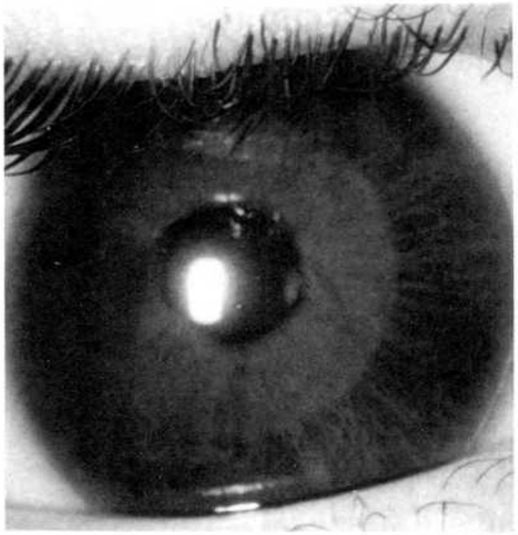

Figure 13 Case II 1. The right eye of this 14-year-old boy has iris hypoplasia, partial posterior embryotoxon, a few peripheral iridocorneal adhesions, and a vision of 6/9.

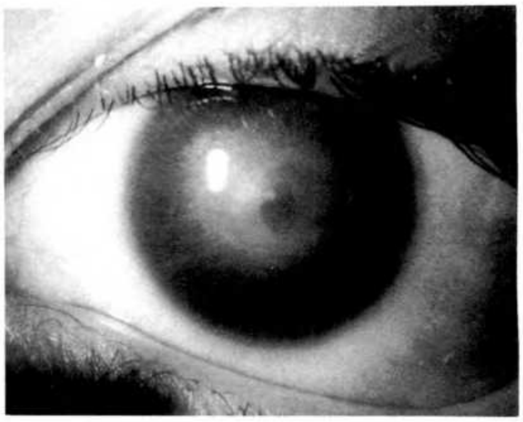

Figure 14 Case II 1. The left eye has Peters' anomaly with a central corneal opacity and a few peripheral iridocorneal adhesions. The vision is counting fingers.

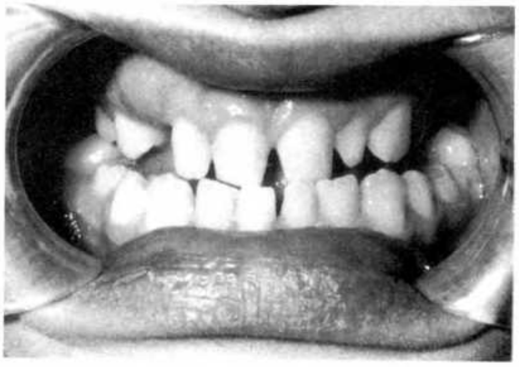

Figure 15 Case II 1. This boy has maxillary hypoplasia, evident by the malocclusion of the teeth. He has also two frontal, capped teeth, two hypoplastic premolars in the lower jaw, and a tiny lateral incisor in the upper jaw.

II 3

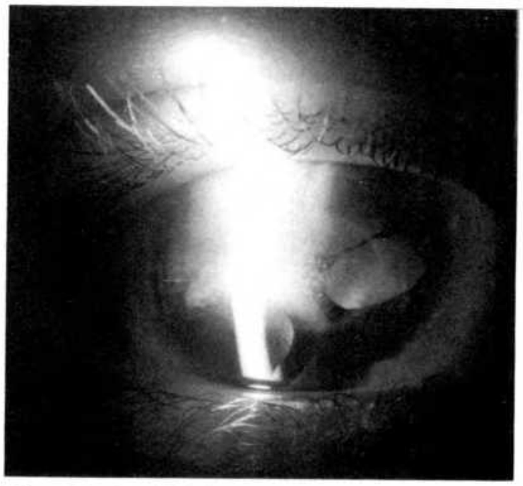

Figure 16 Case II 3. A 7-year-old boy with a right eye with iris hypoplasia, posterior embryotoxon, polycoria, cataract, band keratopathy, glaucoma, and no perception of light.

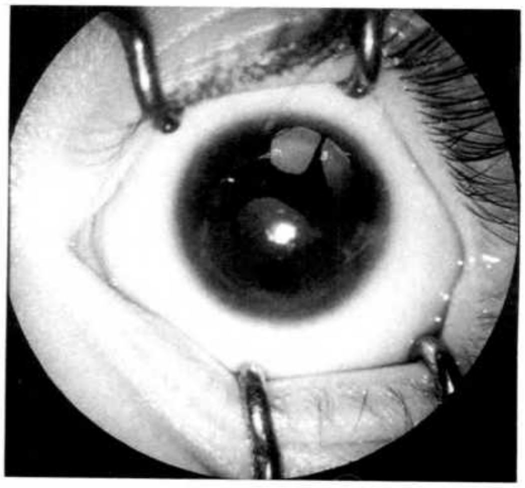

Figure 17 Case II 3. The left eye has iris hypoplasia, posterior embryotoxon, peripheral iridocorneal adhesions, and a vision of 6/9.

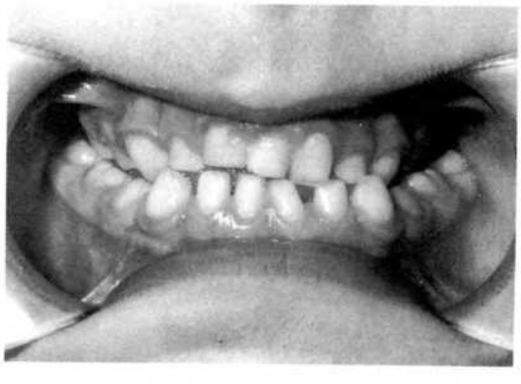

Figure 18 Case II 3. This boy has a bilateral cross-bite, which could be related to a maxillary hypoplasia. His dention is primary, and nothing can yet be said of his permanent teeth.

*Family 3*

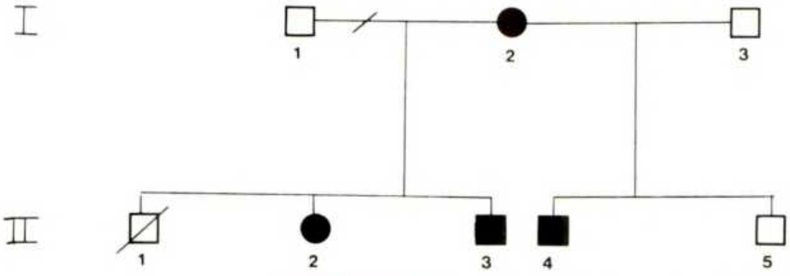

*Figure 19 Pedigree data of family 3.*

*Case I 2. The mother has bilateral iris hypoplasia and partial posterior embryotoxon and normal vision.*

*Case II 2. A nine-year-old girl has bilateral iris hypoplasia and posterior embryotoxon laterally and a normal vision.*

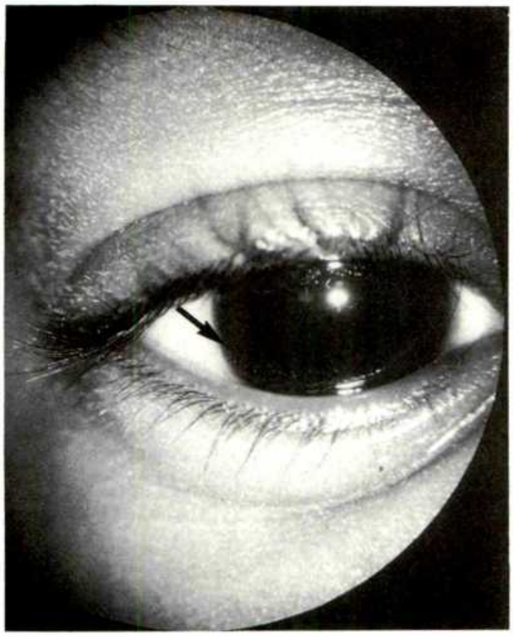

*Figure 20 Case II 3. This 7-year-old boy has a right eye with iris hypoplasia, posterior embryotoxon (arrow), and a normal visual acuity.*

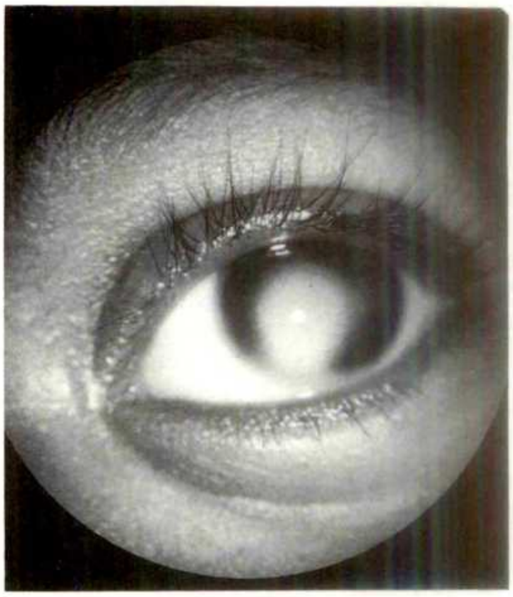

*Figure 21 Case II 3. The left eye shows Peters' anomaly with a central corneal opacity, lens opacity, posterior embryotoxon, and glaucoma. There is no perception of light.*

*II 3*

*Case II 4. A two-year-old boy who has patchy iris hypoplasia bilaterally. His vision appears normal.*

## Discussion

Anterior segment anomalies are caused by disturbances in the early development of the eye. The optic primordium develops from three different embryonic layers: neural ectoderm, surface ectoderm, and mesoderm (primary mesenchyme).[42] Neural crest cells, a subpopulation of cells emigrating from the dorsal margin of the neural folds at about the time of neural tube closure, migrate into the primary mesenchyme to form secondary mesenchyme.[43] Subsequently three successive waves of secondary mesenchyme migrate centrally from the rim of the optic cup to form the corneal endothelium and the trabecular meshwork, the keratocytes, and the anterior iris respectively.[44] Johnston *et al*[43] showed that neural crest cells are the major contributor to the development of the corneal stroma, the corneal epithelium, the anterior chamber, the iris stroma, and the sclera in chick embryos, and light and electron microscopy studies on the human corneal endothelium also point to a neural crest origin.[45]

Several theories of the pathogenesis of the different anomalies of the anterior segment have been presented. Alkemade[4] used the term 'mesodermal dysgenesis of the iris and cornea' to describe the pathogenetic mechanism. Reese and Ellsworth[46] believed that anterior segment anomalies were due to faulty cleavage and introduced the term 'anterior chamber cleavage syndrome' to 'include all possible factors such as improper differentiation, absorption, or even shifting or mobilisation of tissue in its developmental stage'. Waring *et al*[18] presented an anatomical description of the anomalies of the anterior segment, based on the 'anterior chamber cleavage' theory, which they called 'a stepladder classification'. However, Kupfer and Kaiser-Kupfer[8] did not find any embryological basis for this explanation of the anterior cleavage syndrome and instead suggested a disturbance of the migration of the three mesenchymal waves from the optic cup, and the term 'mesenchymal dysgenesis' was proposed by Kenyon.[2] Bahn *et al* suggested a classification of corneal disorders based on neural crest origin, where sclerocornea and Axenfeld's, Rieger's, and Peters' anomaly were thought to be caused by abnormal neural crest cell migration.[44] Neural crest cell disturbances also affect other parts of the body, which explains the systemic symptoms sometimes associated with anomalies of the anterior segment of the eye.[8]

In the families described here the common feature in all three pedigrees is Peters' anomaly in at least one family member. Other affected family members showed Rieger's anomaly, sclerocornea, and other manifestations of anterior segment malformation. Although described in association with a wide variety of extraocular abnormalities,[38] Peters' anomaly is thought to occur most often as an isolated, nongenetic condition.[2] However, there are some cases which are indisputably familial, and these are mainly composed of multiple affected siblings suggestive of autosomal recessive inheritance.[4 47 48] However, dominant inheritance has also been shown,[49 50] and, although single cases of Peters' anomaly have been associated with different chromosome defects including chromosome 4 abnormality,[51] ring 21 chromosomal abnormality,[51] and interstitial deletion of the long arm of chromosome 11,[52] a chromosomal basis is very unlikely to account for most cases.

Axenfeld's anomaly has been reported to be inherited as an autosomal dominant condition.[31] However, Brear and Insler did not find any inheritable basis of Axenfeld's anomaly at all.[53] Sclerocornea is most often thought to be a sporadic or dominantly inherited condition.[10-12] A recessive inheritance pattern has, however, also been mentioned.[11]

Most published evidence points to Rieger's syndrome being inherited as an autosomal dominant condition with a substantial variation in expressivity.[4 19 24 31 34 54 55] However, Forsius[56] found indications of recessive transmission. Rieger's syndrome has been described in association with chromosomal abnormalities, including chromosome 13 deletion,[57] pericentric inversion of chromosome 6,[58] and an isochromosome of the long arm of autosome 6.[59] The genetics of Rieger's anomaly is less clear, though there certainly are pedigrees with autosomal dominant transmission of the eye defect.[22 23] In the absence of an offspring study of isolated cases the proportions due to genetic and other causes cannot be apportioned, and the precise contribution of new mutations cannot be quantified.

The genetic counselling problems in these families are evident from pedigree 3, where the mother (I2) had subtle abnormalities confined to the eyes but her children, who might have been predicted to be at low risk, have inherited Rieger's and Peters' anomalies. In pedigree 1 the mother's eye problems are mainly microcornea and cataract, and yet she is obviously a gene carrier whose children have Peters' and Rieger's anomalies. Even with the lesson of pedigree 3 in mind it would have been very difficult on seeing this woman to have predicted a 50% offspring risk for her. In view of the hypodontia in pedigree 2 it is easier to say that the condition in this family is Rieger's syndrome. However, the mother's (I2) problems are very subtle, and, as with pedigrees 1 and 3, accurate predictions as to the offspring risk would have been very difficult before the birth of her first affected child.

It is probable that the mothers in each of these three pedigrees are gene carriers of an autosomal dominant condition for anterior segment anomalies. In pedigrees 1 and 3 the lesions are without extraocular abnormalities, like the pedigrees reported by Fitch and Kabak[31] and Pearce and Kerr.[23] The resulting eye defects in our families are remarkably variable, and these three pedigrees serve to emphasise the variability of manifestations that this autosomal dominant gene gives rise to. While further complicating the situation for the genetic counsellor, these pedigrees demonstrate that Peters', Rieger's, or Axenfeld's anomaly may be seen as part of a dominantly inherited condition without extraocular abnormalities. At present in the absence of extraocular abnormalities there is no way of knowing whether isolated Rieger's, Peters', or Axenfeld's anomalies confined to the eye are part of Rieger's syndrome, and therefore likely to be transmitted to offspring, or not. This genetic counselling dilemma awaits the outcome of linkage studies and the development of gene specific probes for Rieger's syndrome.

We thank Mr J Dart for endothelial studies of family 2 We are also grateful to the Photographic Department for their help and for support from 'Help a child to see'

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# Macular colour contrast sensitivity in ocular hypertension and glaucoma: evidence for two types of defect

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## Abstract

**Colour contrast sensitivity (CCS) of a large cohort of glaucomatous patients, ocular hypertensive patients (OH), and normal persons was measured at six-month intervals during a two-year period. The OHs were graded into high, medium, and low risk groups. 69% of glaucomatous patients and 32% of all OHs had CCS thresholds greater than the mean plus 2 SDs of the controls. Satisfactory specificity and sensitivity could not be obtained by adjusting the criterion of threshold. In abnormal eyes, progressive small increases of threshold occurred during the study, but glaucomatous eyes with normal thresholds on the first visit retained normal thresholds in the subsequent visits. Although our system is very sensitive and precise, the proportion of abnormalities detected is no greater than with other techniques. In some glaucomatous patients there is a true preservation of colour vision which does not merely reflect the limitations of the test employed.**

Acquired dyschromatopsia can occur early in the course of glaucoma. A blue-yellow loss of colour vision is usually found and may be apparent before nerve fibre bundle defects are detected or visual field defects found.[1] In addition it has been shown that some eyes with ocular hypertension (OH) also have a similar defect.[2 3] Drance[4] reported a colour vision loss in 20% of cases of OH and suggested that testing colour vision could help to identify those who are likely to develop glaucoma. However, some glaucoma patients never show abnormal colour vision, and conversely some OH patients who have abnormal colour vision never develop glaucoma.[4] These discrepancies might either reflect limitations in testing techniques or the complex relation between mechanisms of loss of colour vision and the increase in intraocular pressure (IOP). In principle a distinction could be made between these classes of hypothesis if a more sensitive test of colour vision were to be available.

Colour vision techniques used in clinical practice include the Ishihara test, AO pseudoisochromatic plates, 100-hue Farnsworth and its derivatives, and the anomaloscope[5–9] (for a review see Hart[10]). Another technique which has been used to assess colour vision changes, especially in patients with glaucoma, is colour perimetry.[11–13] Such tests tend to confound luminance with colour increments. The latest results suggest this technique is superior in OH[14] to conventional achromatic perimetry.

Colour contrast sensitivity (CCS) measurements, recently introduced,[5 15] measure true hue discrimination. In CCS the test and the surround have the same luminance and differ only in chromaticity. Such tests have been made possible by recent advances in video and computer technology. In this work we used such a new system which has been fully described elsewhere.[16] Our system proved that abnormalities can be detected in very mild disease,[17] and preliminary results suggested that it could discriminate between ocular hypertensive patients and glaucomatous patients and the normal population.[18] We have tested this hypothesis by measuring colour vision in three different classes of OH patients classified in ways which are known to separate the groups into differing rates of conversion to glaucoma.[19–21]

## Material and methods

### CLINICAL EXAMINATIONS

Patients' eyes were examined by biomicroscopy, funduscopy, disc photography, applanation tonometry, and Humphrey perimetry, and classified by the usual criteria as suffering from either glaucoma or ocular hypertension. Glaucomatous eyes had a visual defect consisting of one locus of sensitivity loss of 10 dB or greater flanked by at least one or more adjacent spots of 5 dB depression. This observation had to be made on at least two occasions. Hypertensive eyes were further classified into three groups by Yablonski's criteria.[22]

### COLOUR VISION TESTS

Colour contrast sensitivity was measured by a system fully described elsewhere.[16] In brief, a computer-graphics peripheral controls the image on a high quality monitor. A program calculates the relative voltages required to produce any colour (within the limits imposed by the TV phosphors) in terms of the CIE 1931 diagram of colour space. Hues were modulated along colour confusion lines for trichromatic vision. Thus protan, deutan, and tritan 'colour axes' were used. The program produces gratings (or other images) in which there is no spatial variation of luminance, and changes in colour contrast are the only clues to image recognition.

To improve precision, individual variations from the CIE (Commission Internationale d'Eclairage) standard observer are first measured. The patient makes a heterochromatic flicker brightness match between red and green and blue and green TV guns. This match is compared with that of the normal observer. The

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*Table 1 Mean tritan thresholds for all classes – first visits*

| *Class* | *Age* | *Protan (%)* | *Deutan (%)* | *Tritan (%)* |
|---|---|---|---|---|
| Glaucoma (n=2) | | | | |
| Mean | 57 | 11 | 11 | 19 |
| SD | 14 | 6 | 8 | 16 |
| High risk (n=59) | | | | |
| Mean | 56 | 8 | 8 | 10 |
| SD | 10 | 3 | 4 | 4 |
| Medium risk (n=56) | | | | |
| Mean | 56 | 7 | 8 | 10 |
| SD | 11 | 3 | 2 | 4 |
| Low risk (n=54) | | | | |
| Mean | 53 | 7 | 8 | 9 |
| SD | 9 | 3 | 2 | 3 |
| Control (n=29) | | | | |
| Mean | 42 | 5 | 6 | 7 |
| SD | 14 | 2 | 2 | 2 |

output is then adjusted to produce equiluminous colours for the patient tested, compensating for his lens changes or macular pigmentation. A square wave grating of 0·6 c/degree filling 25% of the screen was the image. At such a low frequency CCS is not affected by reduced visual acuity. The surround was a mixture of the two colours of which the grating was composed. When colour contrast was 0, all parts of the grating had the same hue as the background. A maximum contrast of 100% was arbitrarily defined as most extreme colours in the 'colour axis' displayed. Gratings appeared once a second for 200 ms. Threshold determinations were carried out monocularly by the method of ascending limits. An increment of 0·01 of maximum contrast was used. The computer produced a warning tone when the staircase began. The patient held a 'mouse' and pressed its button when the grating appeared. The colour contrast was then reduced by a randomly selected amount to a subthreshold value and rose again following a new warning tone. At least three determinations were averaged to obtain a threshold. The computer calculated the mean threshold and its standard error.

### ELECTROPHYSIOLOGY: PATTERN ELECTRORETINOGRAPHY

The PERG was recorded in ways described in other reports.[23] Briefly, a gold foil electrode was used to record from the cornea, and the reference was on the temple. 96% contrast 30′ squares were used, reversing at 3 Hz. About 1000 responses were averaged.

### PATIENTS

All the patients and normal subjects had a visual acuity of 6/6 or better and did not suffer from any other ocular diseases, particularly cataract or corneal disease. The patients were tested during 24 months at six-monthly intervals. They were part of a cohort who are being investigated in several clinical trials.[18 24 25] Normal persons were patients' relatives or hospital staff.

## Results

### PATIENTS WITH GLAUCOMA

Thirty two eyes with early glaucoma were tested on the first visit. Twenty four were tested on two occasions, 16 on three, and 10 on four.

The glaucomatous patients' thresholds (obtained for colour contrasts along the three colour confusion lines) on the first visit are shown in Table 1. It can be seen that the mean threshold was increased by comparison with all OH groups or the control group, the difference being more evident in the tritan axis. Therefore further analysis is restricted to this colour combination. Fig 1 shows the distribution of thresholds in the tritan axis. There was a large overlap in the distribution of thresholds between the glaucoma group and the others, but the distributions for glaucomatous patients and high risk were skewed to higher values, to a much greater extent than for the other groups.

Mean tritan threshold was 19% for glaucoma and 7% for normal persons. A large proportion of the glaucomatous eyes (69%) deviated from the control group mean by 2 standard deviation or more.

The value of testing colour vision depends on the sensitivity and specificity of the test, and this is shown in Fig 2 for the tritan threshold. The discrimination obtained between normal and glaucomatous eyes varied with the colour contrast, which is considered to be abnormal. Fig 2 shows the effect of altering the criterion value in intervals of 1% from 4 to 11%. If the low threshold is considered to separate the normal from the abnormal, there were many false posi-

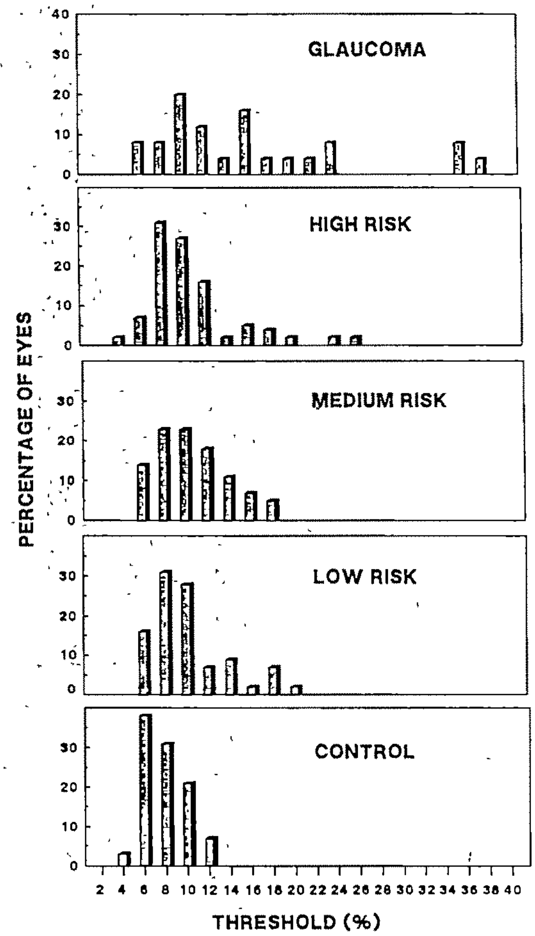

*Figure 1 Distribution of tritan thresholds of colour contrast sensitivity. Maximum colour contrast consisted of a background of (X=0·443, Y=0·445) on which letters were superimposed with a colour of (X=0·302, Y=0·223)*

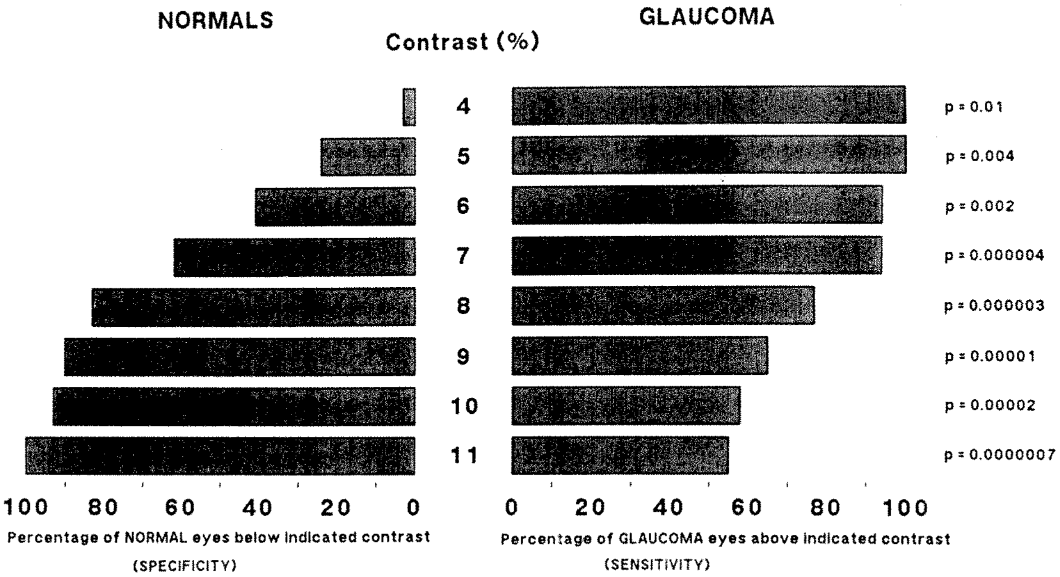

*Figure 2 Analysis of results of colour contrast sensitivity in the tritan axis. Numbers in the middle of the graph represent the range of modulation contrast in which there was overlap between glaucomatous and normal eyes. Bars to the right show percentage of glaucomatous eyes above the indicated contrast. Bars to the left shows the percentage of normal eyes below the indicated contrast. Values of p for each cut-off are from Fisher's exact test. 8% gives the best combination of specificity and sensitivity.*

tives, but all glaucoma patients were considered abnormal. If the criterion is set high, then there were very few false positives, but nearly half the glaucoma patients were false negatives. Thus the length of the bars on the left in Fig 2 represent the specificity, and the bars to the right the sensitivity. Values of p (Fisher's exact test) are indicated for each cut-off level. The best sensitivity and specificity are obtained with a cutoff of 8%, which is similar to the previously determined upper limit of normal. Statistically the results are highly significant. However, 23% of glaucomatous eye would be considered normal by this criterion. This result is not due to the imprecision in the test. For low and medium risk patients who were seen three or more times the difference between tests was less than 1%. If this is taken as an index of test-retest variability (and see Fig 4), there was during the investigation a progressive loss of sensitivity in glaucoma patients, whose mean threshold increased by 2% between the first and second visit and by >1% between the second and the third.

The tritan thresholds for all visits are shown in Table 2. Since patients were recruited during the period of the investigation, the number of eyes progressively decreased with visit number, which precludes comparison between columns.

*Table 2 Mean tritan thresholds for all classes – four visits*

| *Class* | *1st visit* | *2nd visit* | *3rd visit* | *4th visit* |
|---|---|---|---|---|
| Glaucoma | | | | |
| Mean | 19 | 18 | 14 | 14 |
| SD | 16 | 14 | 7 | 7 |
| Number | 32 | 24 | 16 | 10 |
| High risk | | | | |
| Mean | 10 | 10 | 11 | 11 |
| SD | 4 | 3 | 3 | 4 |
| Number | 59 | 44 | 44 | 30 |
| Medium risk | | | | |
| Mean | 10 | 9 | 9 | 10 |
| SD | 4 | 5 | 4 | 2 |
| Number | 56 | 43 | 31 | 23 |
| Low risk | | | | |
| Mean | 9 | 10 | 10 | 10 |
| SD | 3 | 3 | 4 | 5 |
| Number | 54 | 49 | 34 | 21 |

However, if the mean of thresholds of the eyes seen on three visits are considered (n=16), the variation between the three visits is less than 2%.

Because some glaucomatous eyes have normal colour vision, we examined the results to see if any other clinical features were related to this finding. However, neither age, sex distribution, cup/disc ratio, or distance of the field defect from fixation or its size is related to a loss of central colour vision (data not illustrated). The incidence of congenital tritan defects in the population is so low (<1 in a million) that this need not be considered.

### HIGH RISK OCULAR HYPERTENSIVES

Fifty nine eyes with high risk hypertension were tested on the first visit, 44 were tested on two occasions, 41 three times, and 30 on four occasions (Table 1). The thresholds obtained in the three colour confusion lines for high risk OH patients on the first visit are shown in Table 1. Thresholds were lower than glaucomatous eyes' thresholds but slightly above the mean threshold of the control group. Fig 1 shows the distribution of thresholds in the tritan axis in this group. Different criteria of abnormality were again considered, and Fig 3 shows the number of patients who scored abnormal and the number of controls who scored normal for each level. Values of p (Fisher's exact test) are indicated. If the 8% level is taken as cut-off (as in the glaucoma group) 50% of eyes would score abnormal. Although the p values are significant, they are much larger than for glaucoma patients. The variation in thresholds for successive visits in high risk patients was small (Fig 4). Thus the test-retest variation contributed almost nothing to the variability of the results.

The mean threshold of all eyes in each visit (Table 2) was nearly the same, and the variation of mean threshold of eyes seen on three visits (n=41) confirms a variation of less than 1%. Thus comparison of Figs 2 and 3 suggests that the

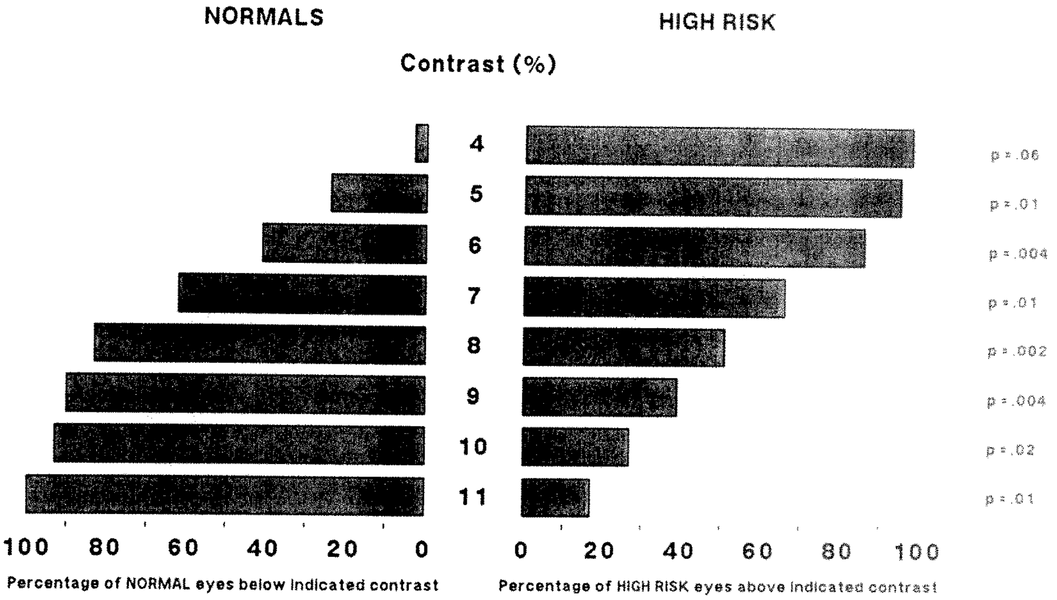

*Figure 3 Analysis of results of CCS in the tritan axis of high risk OH patients. Numbers in the middle of the graph represent the range of modulation contrast over which there was overlap between high risk OH and normal eyes. Bars to the right shows the percentage of high risk OH eyes above indicated contrast. Bars to the left shows the percentage of normal eyes below the indicated contrast. Values of p for each cut-off level are from Fisher's exact test.*

specificity and sensitivity were similar for the two groups.

### MEDIUM RISK GROUP

Fifty six eyes with medium risk hypertension were tested in the first visit, 43 were tested in two visits, 32 in three, and 23 in four visits. The means of thresholds obtained in the three colour confusion lines for medium risk OH patients on the first visit are shown in Table 2. Tritan thresholds were slightly more impaired than protan or duetan and similar to those from high risk patients. The distribution of tritan thresholds almost overlapped that of normal persons (Fig 1).

### LOW RISK GROUP

Fifty four eyes in this group were tested in the first visit, 49 were tested on two occasions, 34 in three, and 21 in four. Table 1 shows the mean thresholds for each colour obtained in the low risk eyes on the first visit. Mean thresholds are not significantly different from those of the normal persons and the other hypertension groups. The distribution of results of eyes with low risk was similar to that obtained in the control group (Fig 1). With 8% taken as a cut-off 43% of low risk would be considered abnormal. The measurements of tritan thresholds for all visits are given in Table 2. Variation of mean thresholds of eyes seen on three visits ($n=34$) was within 1% (Table 2).

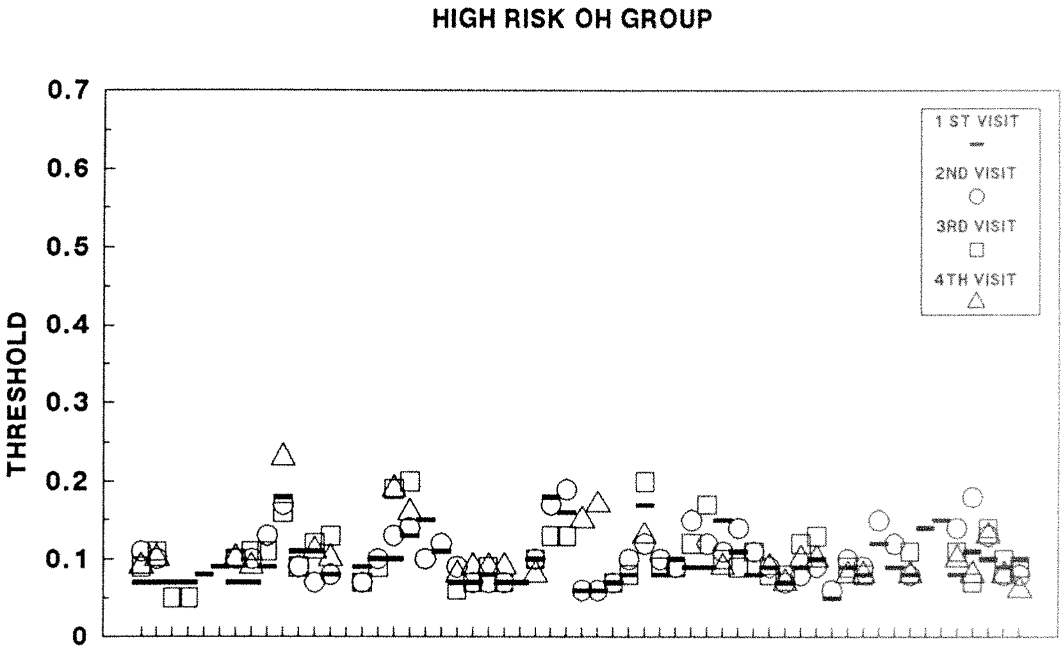

*Figure 4 Results of CCS in high risk group at four visits (tritan axis). Note that there is slight deviation towards higher values. Each division on the x axis represents a different subject.*

### CORRELATION BETWEEN TRITAN COLOUR VISION AND THE PATTERN ERG

The relationship between PERG amplitude (from the peak of P50 to the trough of N95) was investigated for all patients with OH and glaucoma. The results (not illustrated) showed a scattergram with little apparent correlation (r=0·31 for 583 pairs of measurement). However, in 139 cases both tests gave normal results, and in 202 both gave abnormal results. The colour test was normal in 77 cases with abnormal PERG, and abnormal colour vision occurred in 161 cases with a normal PERG. This result is very similar to that of Trick *et al*,[26] who used the Lanthony desaturated D15 colour test.

## Discussion

We studied a large population of ocular hypertensives at different risks of conversion to glaucoma, glaucoma at an early stage, and normotensive glaucoma patients every six months during a two-year period. Combining all the different OH classes, we found the mean tritan threshold to be greater than for the control group, and 32% of all hypertensive eyes had a threshold elevation which deviated more than 2 SD from the mean of the control group. These OH eyes with abnormal colour vision may represent the fraction of OH prone to develop glaucoma. This has been demonstrated in a prospective study.[9] Thresholds in protan and deutan axes are also greater in high risk than in low risk OH, but the difference is less evident than for the tritan results. A significant reduction in colour vision was demonstrated in glaucoma patients for all three colour axes.

However, a considerable overlap exists between the patients and the control population. The value of 2 SDs above the control population did not completely discriminate the glaucoma patients from controls. Our results are in agreement with others in that some glaucomatous eyes never develop loss of central colour vision. Though our system is much more sensitive than other colour vision tests, the proportion of normal results is the same as previously reported. The results of this investigation contrast with that of another study from our clinic, which shows that contrast sensitivity when measured in the peripheral retina to luminance contrast,[25] and especially colour contrast,[27] is universally reduced in an area within 10° to 25° from the fovea in all glaucomatous eyes and in 50% of high risk hypertensive eyes.

Thus there seem to be two patterns of colour vision loss in glaucoma. In one the defect stops short of the macula, while in the other it is diffuse. Thus our data support the concept of two distinct types of mechanism of damage, one leading to diffuse and the other to focal damage in the optic nerve.[28 29] The poor correlation between central colour vision and PERG findings can also be explained on the basis of two types of glaucomatous loss, for the PERG is largely produced by peripheral retinal stimulation and by a system that is not responsive to colour contrast.[30]

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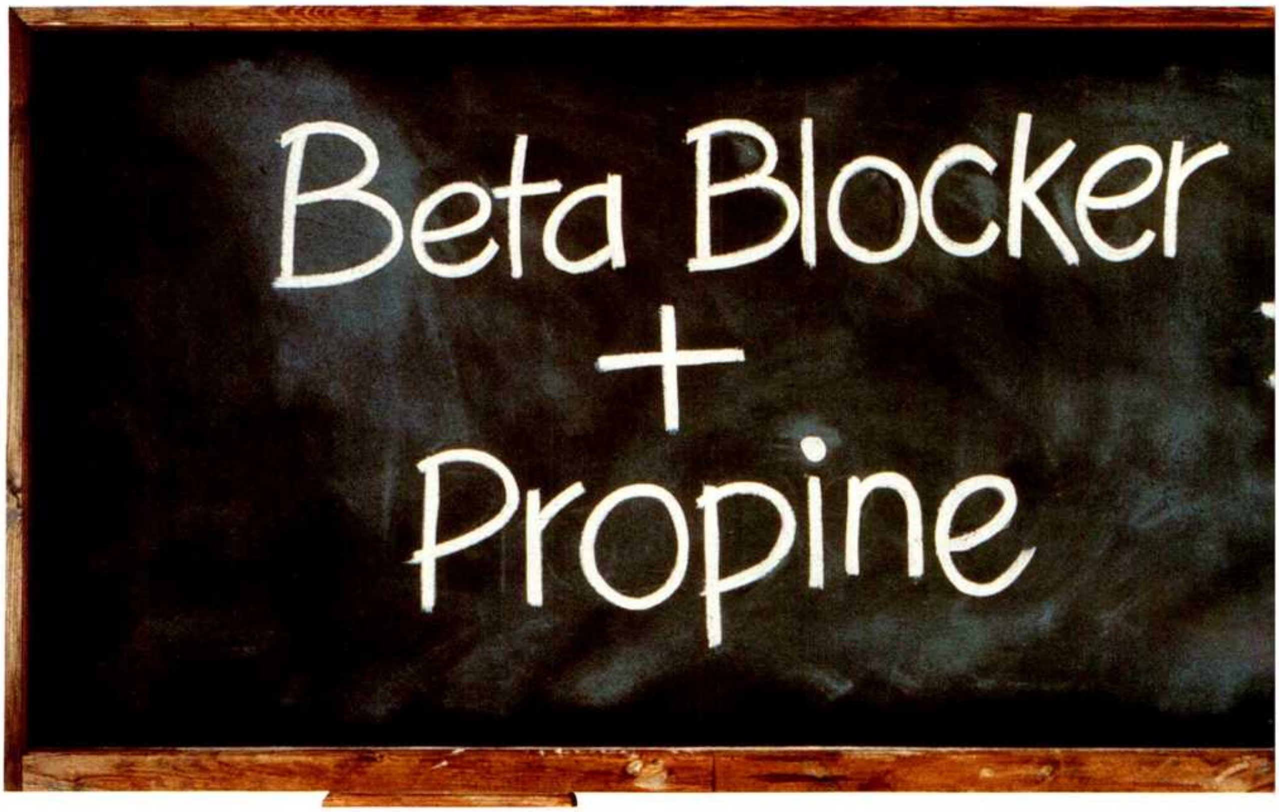

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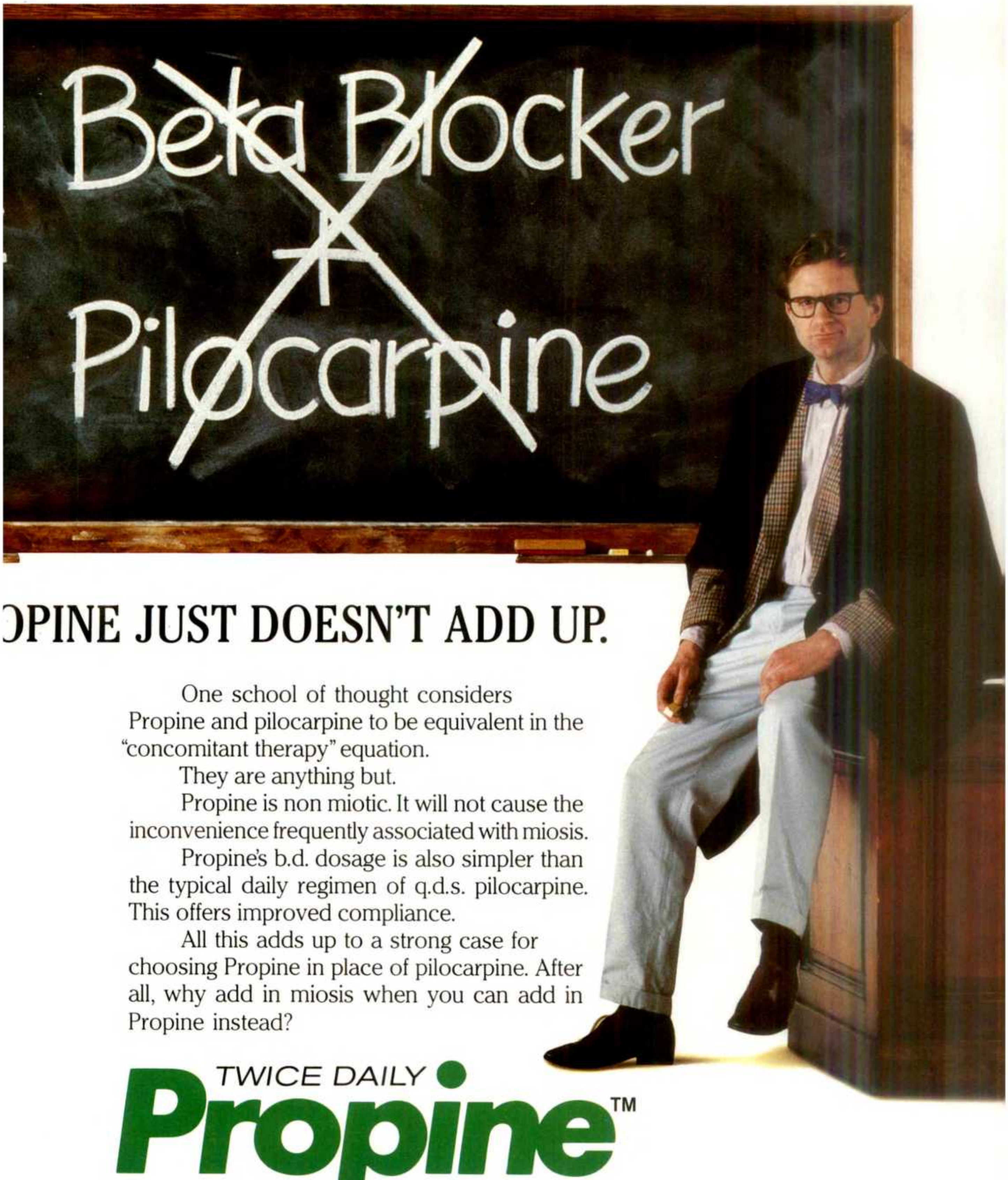

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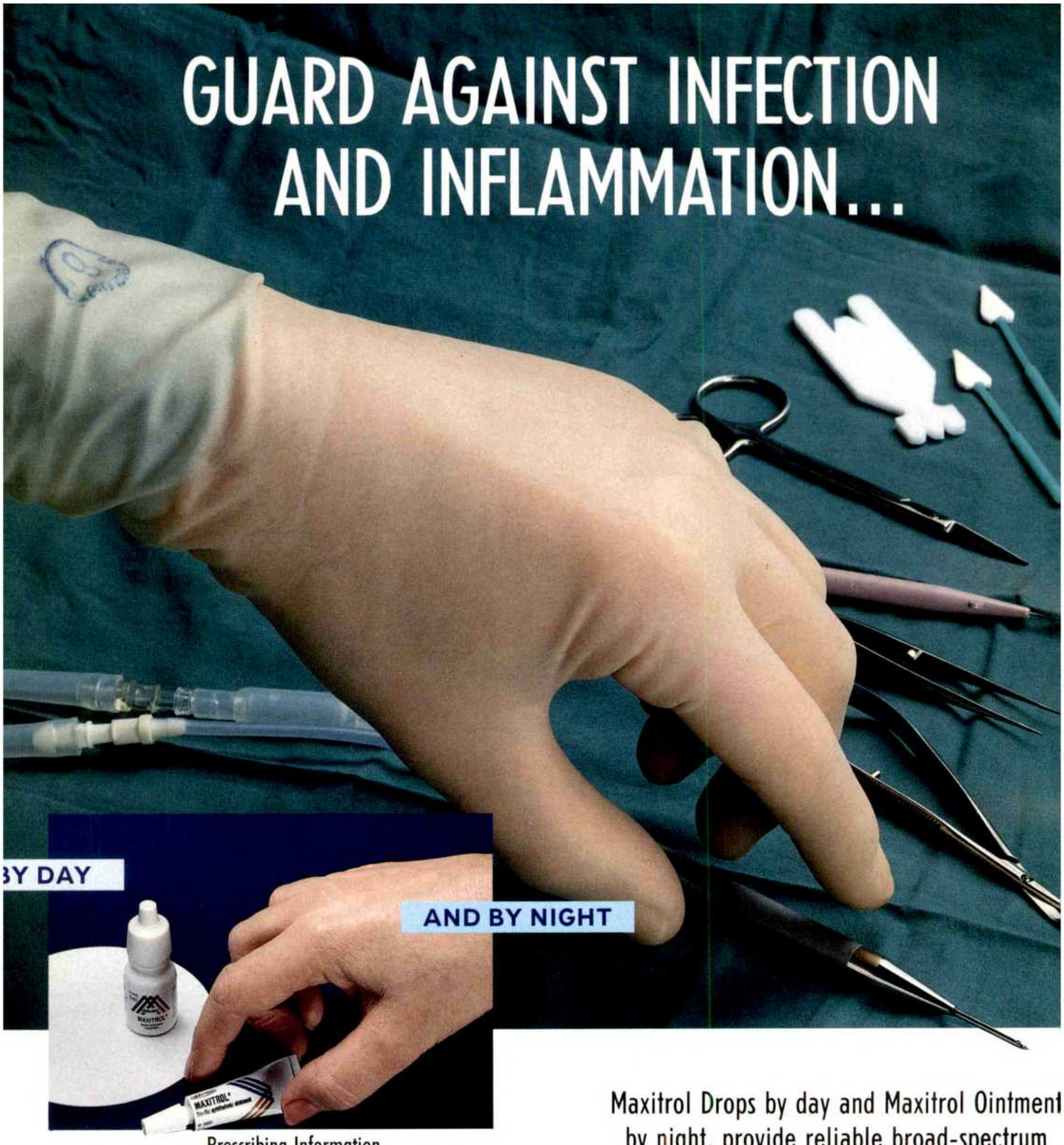

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# High correlation between absolute psychophysical threshold and the scotopic threshold response to the same stimulus

Stuart L Graham, Vaegan

**Abstract**

**The scotopic threshold response (STR) is a negative potential to low intensity light recorded from the dark-adapted retina. It reflects inner retinal function. The STR is now recorded routinely as part of our electroretinography protocol. The projected absolute threshold calculated from the amplitude versus intensity function for the STR has been found to correlate well (r=0·59) with the absolute subjective threshold to the same stimulus. The correlation holds for about 1·5 log units above normal. With further elevation the STR is usually abnormal or absent as b wave threshold is approached. The correlation would have been much greater were it not for this truncated range over which both are recordable. This report includes our findings in 127 patients and examines several disease groups. When the STR had a reduced and abnormal intensity series or was absent, the subjective threshold was elevated in almost all cases (92·2%). The converse relationship also held. When there was a discrepancy, recording problems were usually identified. Since the STR requires difficult, time consuming signal averaging for reliable recording, it may be adequate to record the subjective threshold alone to provide a relatively easily recordable indicator of inner retinal function. Additional STR recording will seldom be warranted.**

The scotopic threshold response (STR) has been shown in man to be a unique component of the normal electroretinogram (ERG).[1-3] It is a negative potential in response to the onset of illumination of intensities ½–2 LU above absolute threshold. It occurs below the b-wave threshold, is dependent on rods at dim illumination, and probably reflects inner retinal function.[4-6] Its origin has been proposed as being amacrine cells,[3] and it has been reported as abnormal in diseases affecting the inner retinal circulation such as diabetic retinopathy.[6] Since it is rod driven, it is also lost in disorders such as retinitis pigmentosa (RP), though its behaviour in the early stages of the disease has yet to be defined.

We have noticed that a raised absolute subjective threshold (recorded to blue strobe flash at the depths of dark adaptation) is usually seen in conjunction with an abnormal STR recorded with the same coloured flashes. The projected absolute threshold, obtained by extrapolating from the STR intensity series, shows good correlation with the subjective threshold, and this relationship holds in all disease groups tested. The significance of this is that the subjective absolute threshold is a relatively fast and reliable test to perform, in contrast with the STR threshold. Each STR is a small signal (<15 μV), and several prolonged averages must be obtained at each intensity before the threshold can be estimated. The subjective absolute threshold may therefore be a simpler addition to the electroretinography protocol than the STR and provide further information on the integrity of inner retinal function, especially when combined with examination of other inner retinal parameters such as the oscillatory potentials (OPs) or pattern electroretinogram (PERG).[7-10]

## Material and methods

We examined 127 patients from Prince of Wales Hospital Eye Clinic and from routine referrals to our electrophysiology unit. Before recording began the patients' pupils were dilated to at least 8 mm with tropicamide 1% (Mydriacil) and phenylephrine hydrochloride 10% (Neosynephrine).

### SUBJECTIVE THRESHOLD RECORDING

The subjective threshold of each eye was recorded after a minimum of 20 minutes of dark adaptation in response to a blue strobe flash. The flashes were presented every 5 seconds, and intensity was initially set at −6·3 log units. One eye was patched while the other was tested. The patient was asked to count consecutive flashes. The flash intensity was raised or lowered according to the patient's response in 0·3 log unit increments. This was sufficiently coarse for us to usually find a 'threshold' level, where detection was 100% and detection 0·3 LU dimmer was near 0%. In a few uncertain cases a detection rate of 50% had to be taken as the threshold.

### STIMULUS PARAMETERS

Subjects were positioned on a chin rest with their faces 2 cm from the centre of a 61×61 cm milk plexiglass screen 5 mm thick. In control experiments (Vaegan, Arora, and Millar, unpublished observations) we verified the report of Arden *et al*[11] that the screen in this position gave ERGs indistinguishable from those obtained with a ganzfeld. An industrial quality stroboscope (IEL, Melbourne, Model XD) with an 8 inch (20 cm) parabolic reflector 15 cm from the other side of the screen delivered 10 μs white flashes. Two filter wheels were set between the strobe and the screen so that one of three coloured filters (red, blue, or white) could be selected and the intensity could be attenuated in 0·3 LU steps between

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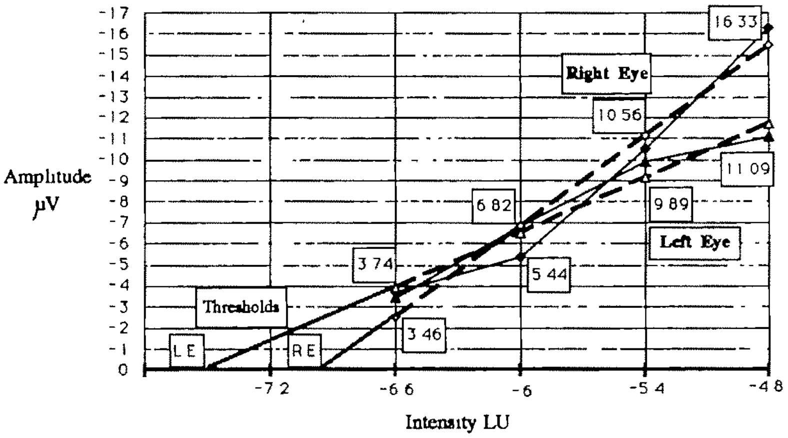


*Figure 1 Example of plotting STR amplitudes and extrapolating an absolute threshold using a line of best fit. The values obtained for each patient were then compared with their subjective thresholds.*

*Table 1 Normal values for absolute subjective thresholds and for STR projected thresholds*

| *Normals* | *STR* | *Subjective threshold* |
|---|---|---|
| No of eyes | 28 | 30 |
| Mean age | 26·8 | 25·5 |
| Threshold | −6·93, SD 0·38 | −6·87, SD 0·09 |
| Gradient | 8·9, SD 3·0 | – |

0 and −6·9 LU (ND filters from Lee, England). Screening was placed so that no light leaked into the room, only that passing through the screen. All STR recording was with the blue filter (Rosco supergel no. 69, brilliant blue, 90% peak transmission at 440 nm, width at half height 380–520 nm, 0% 580–660 nm, red rise to 30% transmission at 740 nm). After attenuation by the blue filter and the screen the brightest flash was 0·305 cd.m$^{-2}$ s$^{-1}$ (8·0 log quanta 450 s$^{-1}$ assuming a 9 mm pupil). Normal ERGs, to photopic white flashes and scotopic blue flashes, saturated at −0·3 LU attenuation and were smaller at 0 LU. Scotopic ERGs to white had a waveform like those expected from a 'standard' flash, as defined in the ISCEV standard.[12] The greatest attenuation used for ERG recording was −6·3 LU or the absolute psychophysical threshold, if it was greater.

STR RECORDING

The eyes were topically anaesthetised with proxymetacaine hydrochloride 0·5% (Ophthetic). After lubrication with a drop of methylcellulose 2% (Methocel) locally constructed gold-foil electrodes[13] (similar to previously published designs but improved by better bonded gold) were placed in the lower fornix. The use of gold foils[11] allowed us to record binocularly for over two hours without evidence of the ocular irritation or corneal oedema that is frequently seen with contact lens electrodes. The indifferent electrodes (3 M red dot), cut to sit close to the eye, were placed at the outer canthus, and another electrode on the central forehead served as the earth. The amplifier had 10 000×gain, and the four-pole Bessel filters included all frequencies between 0·1 and 2 KHz. A PDP 11/23 computer (Digital Electronic Corp), programmed in the DAOS language (Laboratory Software Association, Melbourne) was used for signal averaging, plotting, and measurement.

For the STR, 128 sweeps were averaged at a rate of one flash every 670 ms; the time base was 384 ms. The baseline drift was adjusted by software so that the response had returned to baseline after 384 ms. Latency was chosen from values close to those published by Aylward, Vaegan, and Billson.[2] Minima were chosen between here and 200 milliseconds. Cat STR peak times recorded by Arora, Vaegan, and Miller[14] were used as a guide. It was essential to take special care with noise elimination to ensure reliable recording of small signals like the STR.

*To eliminate mains noise,* timing was driven by a counter, based on a mains signal zero crossing detector to give clock pulses at 2× mains frequency. The averager was triggered after an odd number of zero mains crossings, usually 67, that is, 670 milliseconds, also 2670 to 4670 at higher intensities above b-wave semisaturation. The ongoing high frequency noise was never greater than 100 µV; if higher values were observed, electrodes were examined and corrected and the recording restarted.

*Artefact rejection* was carefully adjusted. In general this can be done in two ways: either varying gain to make a steady signal close to the limits of the artefact rejector or by varying its trigger limits. The first was not available to us because of our fixed gain amplitude. The second was readily accomplished, though with some loss in the number of useful bits in the 12 bit A to D converter. Limits could be dynamically adjusted during the test by setting a single parameter to ensure there were always a few rejections (5%), however good the subject. System noise was ±30 to ±50 µV. The tightest limit was ±75 µV, while the most relaxed was never wider than ±200 µV in the STR range.

*Continuous monitoring of the ongoing signal.* Mains noise and artefacts which suddenly intruded were usually associated with the gold foil sticking to the tear wetted cheek after blinks. Electrodes were readjusted under red light to ensure that the bottom of the gold foil stood off the face (in accordance with Holder[15]). The experimenter and the subject were alerted to the presence of blinks or eye movements by computer beeps. The subject's task was to keep

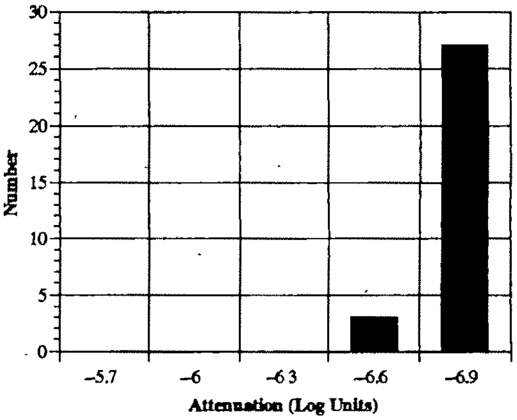


*Figure 2 Absolute subjective thresholds for normal patients. Lower limit of testing was −6·9 LU and almost all patients achieved this level. ■ = Number of eyes tested*

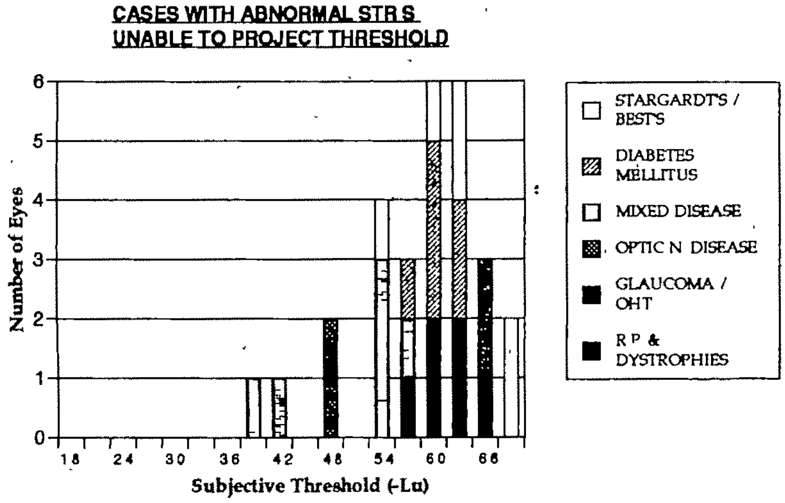
*Table 2 Values for absolute subjective thresholds and for STR projected thresholds in different disease groups. The absent column includes those with a markedly abnormal STR intensity series such that a threshold could not be extrapolated. Note the large number of RP cases and diabetics in this column*

| | | *STR – projected threshold* | | | *Subjective threshold* | |
|---|---|---|---|---|---|---|
| *Disease group* | *No. eyes* | *Absent* | *Mean (−LU)* | *SD* | *Mean (−LU)* | *SD* |
| RP and retinal dystrophies | 52 | 45 | 4·98 | 0·87 | 4·81 | 1·08 |
| Cone dystrophy | 24 | 4 | 6·39 | 0·85 | 6·53 | 0·35 |
| Diabetes | 36 | 18 | 6·03 | 0·69 | 5·65 | 0·87 |
| Pre laser | 22 | 8 | 5·99 | 0·75 | 5·43 | 1·05 |
| Post laser | 14 | 10 | 6·10 | 0·37 | 6·00 | 0·24 |
| CRVOs | 4 | 4 | – | – | 6·38 | 0·29 |
| Glaucoma and ocular hypertension | 24 | 8 | 6·62 | 0·64 | 6·27 | 0·73 |
| Optic nerve disease | 34 | 8 | 6·50 | 0·91 | 6·20 | 0·71 |
| Macular disorders | 14 | 1 | 6·57 | 0·41 | 6·60 | 0·37 |
| Stargardt's disease/flavimaculatus and Best's disease | 16 | 6 | 6·51 | 0·30 | 6·53 | 0·48 |
| Mixed disease | 20 | 8 | 6·88 | 0·65 | 5·87 | 0·85 |

these beeps to a minimum, since each one was associated with a rejected sweep.

*Mains shielding.* The cables for active and indifferent were shielded by the earth lead to within 10 cm of the subject.

The STR amplitudes were plotted against intensity and a least squares estimated straight line was fitted to the monotonically increasing part of the curve. Because the line is fully described by two parameters – gradient (in μV/log unit) and threshold (the zero intercept) – a more complete assessment of the STR function is achieved in the form of a gradient of increasing response and an extrapolated threshold. Figure 1 shows an example using a normal patient.



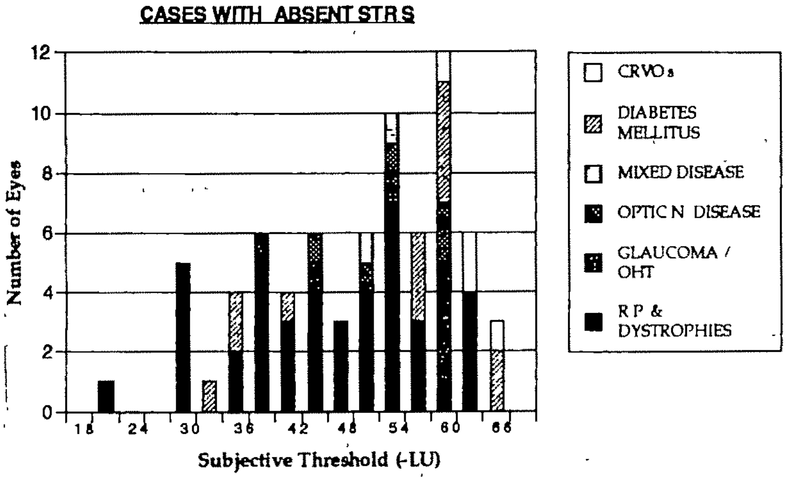


*Figure 3 Charts showing the subjective thresholds in those patients in whom the STR was absent, or reduced such that an absolute threshold could not be determined. Of these patients 92% recorded a subjective threshold above or at −6·3 LU (which is elevated).*

*As expected the STR did not persist in most cases of RP, since it is rod dependent, although it was preserved in most of the cone dystrophies. The previously described finding of its reduction in diabetic retinopathy was observed. It was also absent in CRVO's. No definite pattern of reduction was identified in other disease groups (see Figure 6 also).*

Problems in recording the STR include: (1) The STR can be recorded only across a limited range of intensities (1·5–2 LU). (2) Variable $V_{max}$ and amplitude intensity function due to b-wave intrusion. (3) Confusion with slow PIII (which occurs later and at slightly higher intensities). As a general rule we found that STR peak times were 220 ms at most and became earlier as the response grew larger, whereas slow PIII was always later than 240 ms. When the STR was reduced with an elevated threshold and the b-wave/PIII complex was normal, the STR and slow PIII could be confused. (4) High noise, including eye movements. (5) Problems of fitting lines to a limited series of imprecisely located points to obtain an accurate projected threshold.

## Results

The normal values are shown for patients tested in our laboratory in Table 1 and their distribution in Figure 2. Almost all normal persons achieved a subjective threshold of −6·9 LU, with a lesser number recording −6·6 LU. This gave a mean of −6·87 LU (SD 0·09 LU). For the STR the mean projected threshold for our normals was −6·93 LU (SD 0·38 LU). The results, except for one case, represent recordings made on the same patient at a single recording session.

In Table 2 the results are included for the broad disease groups. Whereas a subjective threshold is always recordable (even if raised significantly), the STR intensity series is often abnormal in disease, and therefore this table includes threshold values only in those patients in whom they were recordable. Figure 3 shows the remaining patients in whom the STR was either abnormal or absent. In all but eight of these eyes the subjective threshold was −6·3 LU or above, which is outside our range for normal persons. Therefore when the STR had either an abnormal intensity series or was absent, 92·2% of eyes tested had an elevated subjective threshold.

The graphs shown in Figures 4 and 5 record the projected ERG thresholds derived from the STR series plotted against the subjective thresholds for each patient, Figure 4 is a summary of all patients where both an STR and a subjective threshold could be recorded. The calculated regression lines have been drawn in.

There is a significant correlation between the two recordings of 0·59. This correlation would have been higher but for two limiting factors. Firstly, the lower limit of our equipment for subjective thresholds was −6·9 LU, and clearly the majority of normal persons were at this level. Had we been able to test for lower levels some of these patients may well have had thresholds of −7·2 LU or less. Secondly, at levels above −5·0 LU, the b-wave begins to intrude on the STR, eventually cancelling it (see Figure 6 for example of normal patient). The patients with thresholds

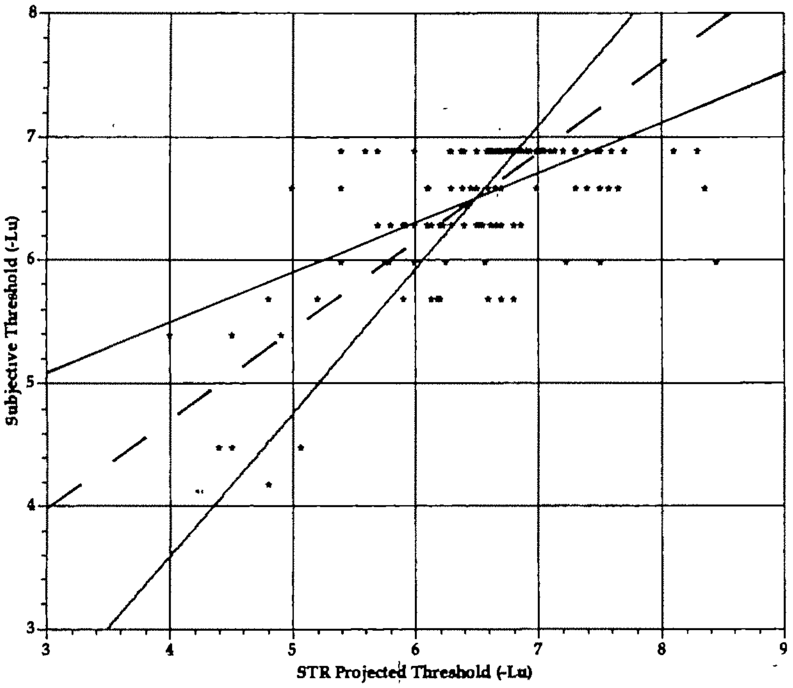


*Figure 4 Summary of all patient groups plotting STR projected threshold against subjective threshold. Linear regression lines are included. Correlation r=0·59. Note the flattened distribution at −6·9 LU representing our lower limit of the subjective threshold recording. Also very few patients are seen to have a recordable STR above a threshold of −5·4 LU. These two factors have limited the correlation achieved.*

elevated into the b-wave range would therefore have their STRs reduced or cancelled, and many of these patients may be seen in Figure 3. A further example of this could be in some RP patients when a delayed b-wave intrudes on the STR directly and cancels it earlier, though we have seen some RP patients in whom the b-wave threshold is also elevated and the STR may be reduced but preserved.

It can be seen from Figures 2, 3, and 4 that if the subjective threshold is above −6·0 LU there is a very high incidence of either an abnormal STR threshold, or of the STR being reduced in amplitude and range, or even absent. There were a few cases of artificially low STR thresholds (<−8·0 LU); also eight eyes recorded a reduced or absent STR at subjective thresholds of −6·6 LU or better. We believe, from examining the traces in these subjects, that they mainly represent STR recording errors with a combination of variable wave forms and incomplete or truncated intensity series, which makes extrapolating a threshold unreliable.

It is not the purpose of this paper to report the various changes of the STR seen in individual diseases. However, in general it can be seen that there were reductions in the STR threshold in diabetes as previously described by Aylward.[6] There were more marked losses in those who had undergone laser treatment, as expected with large areas of retina ablated, but the correlation still held in these patients. There were significant reductions in most cases of RP, which is consistent with widespread rod losses. The STR was also absent in the four central retinal vein occlusions reflecting inner retinal ischaemia. It was preserved in the cone dystrophies.

## Discussion

Our recordings show that, when the subjective threshold is raised, the STR threshold is also raised. This relationship holds for about 1·5 log units, above which the STR is usually abnormal or absent. Conversely, when the STR is of reduced amplitude, abnormal form, or has a raised threshold, the subjective threshold is also abnormal In those few cases in which there was

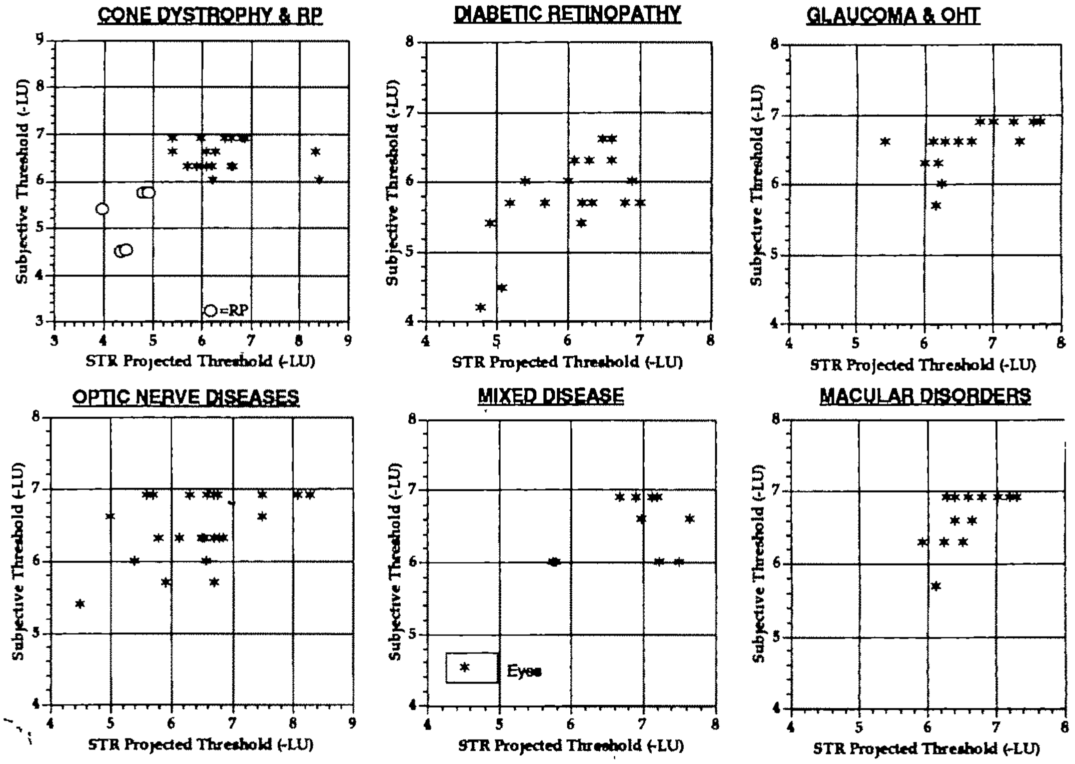


*Figure 5 Individual patient groups showing STR projected threshold plotted against the subjective threshold. Correlation between the two methods seems to hold for different disease groups. The few RP patients who had an STR are shown as circles.*

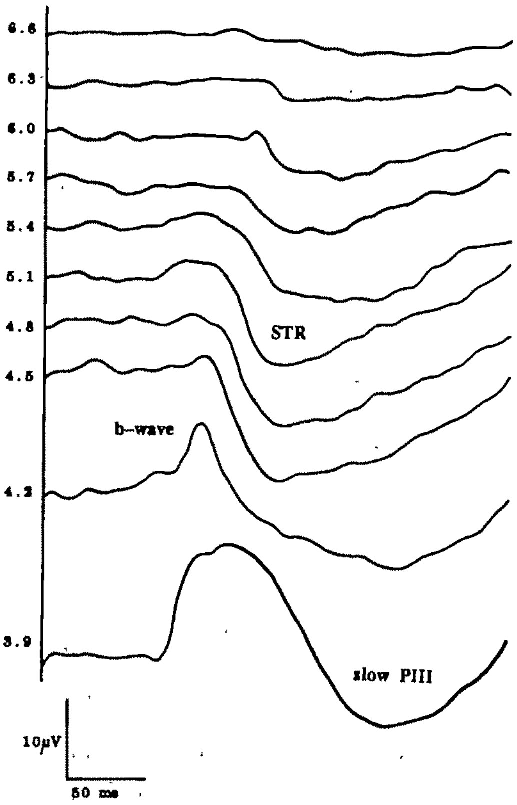


*Figure 6 Example of normal STR intensity series. Note increasing amplitude of STR until b-wave threshold is reached. The STR becomes swamped by the b-wave by −4·2 LU.*

no agreement between the two responses it was usually the STR that was suspicious. We believe that this reflects recording difficulties with the STR rather than a true discrepancy between the responses.

It is clear that a raised subjective threshold is by no means a specific indicator for any one disease process, but shows subtle changes at these very low luminances which seem to reflect a disturbance of the integration of rod responses. This normally occurs in the process of spatial summation at the level of the amacrines, so it is not surprising that diseases that alter the STR (which is thought to originate at this level) will also effect the subjective threshold.

Since the amplitude of the STR is very small (8–20 μV), recording is subject to frequent artefact intrusion and requires multiple sweeps to achieve a reliable trace. At least five traces taking over 15 minutes need to be recorded to ensure there are enough data. Recording the subjective threshold, however, is simple, and the only source of error here is patient confidence in reporting the visual stimulus at low levels. Thus the subjective threshold may be an easy alternative to the STR in co-operative patients and still provide additional information on both rod function – as has been its traditional role in conditions such as RP – and on the state of the inner retina – in diabetic retinopathy or central retinal vein occlusion for example. If a questionable elevated subjective threshold is found, electrophysiological confirmation with an STR intensity series is still possible.

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# Panretinal laser photocoagulation for proliferative diabetic retinopathy: the effect of laser wavelength on macular function

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## Abstract

**The effect on macular function of the wavelength of laser light used to treat proliferative diabetic retinopathy was studied. Thirty-six eyes of 25 patients received panretinal photocoagulation according to a standardised protocol and before and at intervals after the treatment were tested by a battery of macular function tests. Each eye was randomly assigned to treatment with blue-green, yellow, or orange laser. The tests included best corrected visual acuity, colour vision, contrast sensitivity, macular threshold, and central visual fields. There were no significant differences in the results of these tests between the three treatment groups, though there was wide scattering of baseline values within each group. Laser wavelength has not been shown to be an important determinant of central visual function following panretinal photocoagulation in patients with proliferative diabetic retinopathy within the wavelengths tested.**

Panretinal laser photocoagulation is an established and effective treatment for proliferative diabetic retinopathy.[1,2] Argon blue-green lasers have been used most commonly. There is, however, increasing awareness of the potential phototoxic hazards of short wavelength lasers both for the operator[3,4] and for the patient.[5] The aim of the present study was to determine by a battery of macular function tests, whether macular phototoxicity could be demonstrated after panretinal laser photocoagulation, as currently practised, and if so whether longer wavelengths produced less of an effect than others.

## Patients and methods

Patients attending Moorfields Eye Hospital with previously untreated proliferative diabetic retinopathy were invited to participate in the study. Patients were eligible if they had proliferative diabetic retinopathy, either with disc new vessels or with new vessels elsewhere, as assessed by biomicroscopy and fluorescein angiography. Their eyes had a visual acuity of 6/12 or better, a normal intraocular pressure, clear media, no clinically significant macular oedema as defined by the Early Treatment Diabetic Retinopathy Study Research Group,[6] and no other pre-existing ocular pathology. Informed consent was obtained, and the patients agreed to a protocol approved by the Ethical Committee at this institution.

Prior to treatment each patient had a full ophthalmic assessment which included slit-lamp biomicroscopy and binocular indirect ophthalmoscopy. All patients had fluorescein angiography and fundus colour photography prior to laser treatment.

At entry the study eyes were randomised to treatment with one of three wavelengths; blue-green (488/514 nm), dye yellow (577 nm), or dye orange (595 nm). All treatments were carried out on the coherent dye laser. Where both eyes of the same patient were enrolled, one was treated with argon blue-green, and the other was randomly assigned to dye yellow or orange. Follow-up fluorescein angiography was undertaken at the end of the study period (three months) to assess macular perfusion and confirm regression of the new vessels.

The patients were treated through a maximally dilated pupil with a Rodenstock lens. The Goldmann three-mirror lens was also used on four eyes where only partial treatment could be obtained with a Rodenstock lens. The patients were treated in a single treatment session with topical anaesthesia (amethocaine). Two thousand burns were applied to each eye, of spot size 200 μm and duration 0·1 second. In those eyes in which treatment was completed with a three-mirror lens, the spot size was increased to 500 μm. The power was adjusted to produce just noticeable immediate blanching of the retinal pigment epithelium. No additional laser treatment was given during the three-month period needed to complete the study.

The battery of macular function tests described below was done before photocoagulation and then one week, one month, and three months after treatment. All the psychophysical measurements were performed under standard conditions of illumination with the exception of the visual fields. For this investigation the patient was dark adapted for five minutes and then tested under mesopic conditions.

The best corrected visual acuity was recorded on a projected Snellen chart at a distance of 6 metres. Colour vision was assessed with a Farnsworth-Munsell 100-hue test. The error score was calculated from the sum of differences between the number of each cap and its standard position.[7] Contrast sensitivity was evaluated by both the Arden grating and Vistech plates.[8,9] Contrast sensitivities were measured between 0·2 and 6·4 cycles per degree for the Arden gratings and between 0·5 and 22·8 cycles per degree for the Vistech gratings. Macular thresholds were assessed with the Friedmann Mark 1 field analyser from four locations in the central 5°.

The psychophysical data from the three treat-

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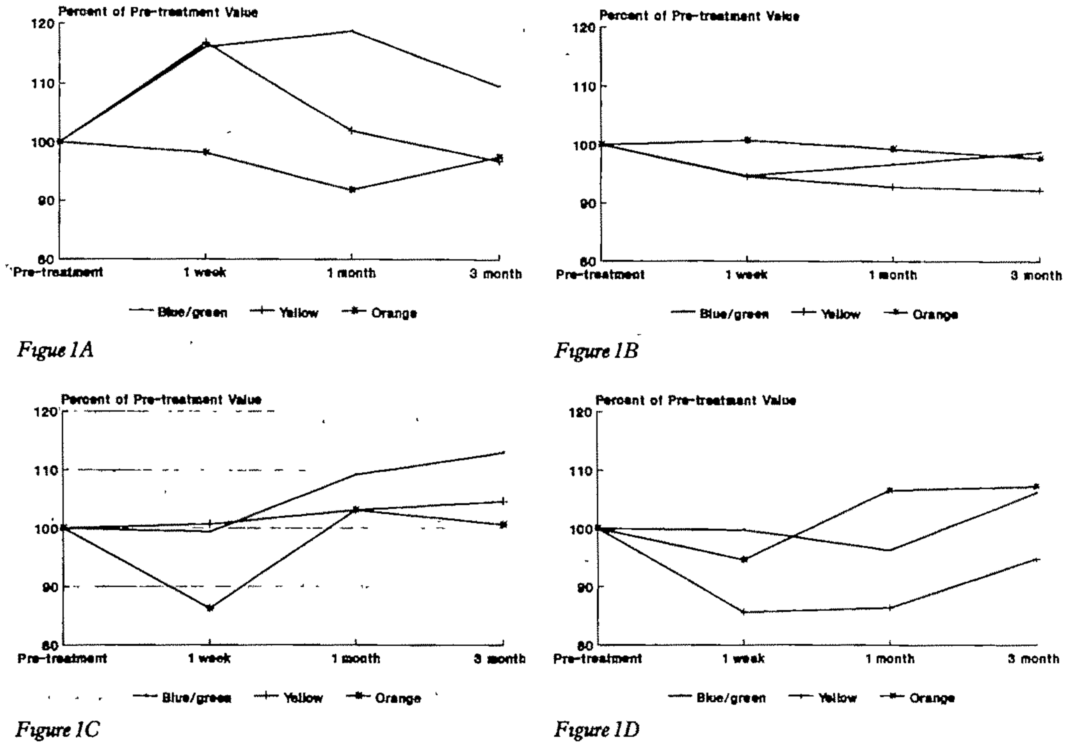

*Figue 1A*

*Figure 1B*

*Figure 1C*

*Figure 1D*

*Figure 1 Results of data from three groups of patients treated with blue/green (488/514 nm), yellow (577 nm), and orange (595 nm). The results are shown as the mean of the post-treatment values as a percentage of the pretreatment value for each test: (A) Farnsworth-Munsell 100-hue test; (B) Arden gratings; (C) Vistech plates; (D) Central field threshold.*

ment groups were compared by a masked observer. With the exception of the Snellen acuity the results were analysed according to the general linear model (GLM) procedure using a split plot design with the program SAS. The data satisfied the requirements of type H covariance, so adjustment factors were neither needed nor employed. In addition separate analysis was made for each psychophysical parameter as a function of time. In this later analysis significant main and interaction effects were investigated by Tukey's HSD ('honestly significant difference'). A significance level of 5% was maintained for all analyses.

## Results

Thirty-six eyes of 25 patients were included in the study. Fifteen eyes were treated with argon blue-green, 10 with dye yellow, and 11 with dye orange. The patient's characteristics in the three treatment groups were similar; their mean age was 48 years (range 20–72 years) and half were women. Sixteen of the patients were insulin dependent, the remainder being controlled with oral hypoglycaemic agents.

*Table 1 Results: value (standard deviation)*

| | *Pretreatment* | *1 week* | *1 month* | *3 months* |
|---|---|---|---|---|
| *Farnsworth-Munsell 100-hue* | | | | |
| Blue/green | 223 (180) | 251 (190) | 240 (166) | 231 (168) |
| Yellow | 254 (141) | 255 (123) | 240 (126) | 237 (139) |
| Orange | 207 (140) | 213 (154) | 206 (154) | 205 (151) |
| *Arden grating* | | | | |
| Blue/green | 81 (13) | 77 (14) | 78 (11) | 79 (10) |
| Yellow | 85 (13) | 80 (15) | 78 (16) | 79 (16) |
| Orange | 79 (7) | 80 (11) | 79 (8) | 78 (10) |
| *Vistech plates* | | | | |
| Blue/green | 17·8 (5·7) | 17·6 (5·4) | 18·6 (4 9) | 19 3 (5·2) |
| Yellow | 16 9 (7·9) | 15·5 (5·8) | 16 3 (6·5) | 16 1 (5·1) |
| Orange | 17·0 (9·0) | 16·9 (5·2) | 19·9 (5·8) | 19·6 (5 8) |
| *Central field threshold* | | | | |
| Blue/green | 2·2 (0·46) | 2·1 (0 39) | 2·1 (0·55) | 2·2 (0·46) |
| Yellow | 2·2 (0·62) | 1·9 (0·71) | 1·9 (0 71) | 2 0 (0·67) |
| Orange | 2·3 (0·40) | 2·2 (0·48) | 2·4 (0·42) | 2·4 (0·32) |

The data presented graphically (Fig 1) have been normalised to show the change of post-treatment values as a percentage of their pre-treatment levels. There is a trend for the Farnsworth-Munsell 100-hue value to be worse after treatment with shorter wavelength laser and to take longer to return to the baseline. Little change occurred pre- to post-treatment in the Arden plate or Vistech data, while in all groups there was a consistent reduction in central field threshold a week after treatment which later recovered. No trend was shown to be statistically significant.

## Discussion

Xenon arc and heavy, long-duration-burn argon blue/green laser panretinal photocoagulation in diabetics have been shown to reduce macular function as measured by the Farnsworth-Munsell 100-hue test.[10 11] There is increasing awareness of the unique sensitivity of the retina to blue light.[12 13] Acute macular phototoxicity after short but not long wavelength laser exposure can be demonstrated in both the operator[3 4] and in patients treated for peripheral retinal tears with previously normal colour vision.[5]

A wide variation was found in the pretreatment values for the psychophysical parameters, particularly colour vision, which made the standard deviations quite large (Table 1). This weakened the statistical comparisons between the three treatment groups.

This study was undertaken to determine whether the use of longer wavelength laser for panretinal photocoagulation could be shown to produce a significantly better macular outcome than argon blue-green laser. Current treatment protocols in panretinal photocoagulation call for short duration (0·1 second or less), light (just visible grey-white spots) burns. The main observation to come out of this study is how poor and variable macular function is even in a group of diabetics with proliferative retinopathy selected for their good pretreatment visual acuity. The standard deviation of the baseline tests was large, and the values themselves were worse than those in non-diabetic patients. Similar changes have been noted before[14 15] and may have been the main factor which prevented demonstration of the more subtle phototoxic effects of shorter wavelength lasers. This may also explain the similarity of outcomes in patients treated by grid photocoagulation for diabetic macular oedema with argon blue-green and krypton red lasers.[16]

This study demonstrates that the diabetic eye is a poor model for the assessment of the clinical side effects of lasers, but the non-significant results as detailed above should not be taken as evidence that short wavelength lasers are as safe as longer wavelength ones. There is gathering proof in favour of longer wavelengths, and it seems advisable to avoid blue laser light wherever possible.[3-5]

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lston J., Marsden C.D. J. Neurol. Neurosurg. Psychiatry 1988;51:767-772. **2.** Elston J.S. 1991 in press. Dysport is a trademark.

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British Journal of Ophthalmology, 1991, 75, 611–614

# Ocular complications of bone marrow transplantation

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## Abstract

**Forty-one patients who had undergone bone marrow transplantation were examined. Nineteen (63%) of the 30 who had received fractionated total body irradiation (TBI) had cataracts in comparison with only 1 (9%) of the 11 non-irradiated patients. No significant differences in steroid therapy were demonstrated between these groups of patients. Dry eyes were observed in eight irradiated patients, seven of whom had preceding graft-versus-host disease. Superficial punctate staining of the bulbar conjunctiva was observed in 25 (83%) of the irradiated group and, in milder form, in five (45%) of the non-irradiated group. Our data suggest that the incidence of cataract following fractionated TBI is influenced not only by the total dose of radiation but also by its rate of administration (defined by midline tissue dose rate and fractionation schedule). In addition dry eyes and conjunctival staining may be exacerbated by TBI, though other aspects of conditioning may also be implicated.**

Bone marrow transplantation (BMT) is an established treatment for haematological malignancy.[1] Patients undergoing transplantation receive conditioning treatment which may include total body irradiation (TBI) to eradicate both tumour and recipient marrow cells. The eyes are not normally shielded during TBI because they are a potential site of leukaemia relapse. After the conditioning treatment patients receive either autologous marrow harvested during apparent remission from disease or allogeneic marrow from a tissue matched donor.

Graft-versus-host disease (GVHD) is a major complication of allogeneic BMT.[2-4] It results from a reaction of immunocompetent donor marrow cells with recipient (host) tissues, and affects principally the skin, gastrointestinal tract, and liver. It may require treatment with large doses of systemic steroids. Ocular complications are common.[5-10]

Transplant patients are consequently at considerable risk of developing cataracts as a result of their exposure both to TBI[8 10] and to systemic steroids.[11] The relative risk to these patients of developing cataract is reported to be significantly reduced by either fractionating the TBI or omitting it completely.[8]

The purpose of this study was to determine the incidence of ocular complications in a group of long term survivors of BMT who had received chemotherapeutic tumour ablation either alone or in combination with fractionated TBI.

## Patients and methods

The study group consisted of 41 adult patients who underwent BMT for various haematological malignancies (Table 1) at the Royal Victoria Infirmary between March 1983 and September 1989.

### TREATMENT GROUPS

*Group 1.* Eleven patients underwent autologous BMT following conditioning with a single dose (3 mg/kg) of melphalan, but no irradiation.

*Group 2.* Thirteen patients underwent autologous BMT following conditioning with a single dose (3 mg/kg) of melphalan followed by TBI. A total dose of 10·5 Gy was given as three fractions of 3·5 Gy over 36 hours.

*Group 3.* Seventeen patients underwent allogeneic BMT following conditioning with two daily doses (60 mg/kg) of cyclophosphamide followed by TBI. A total dose of 12 Gy was given as six fractions of 2 Gy over three days.

TBI was administered by linear accelerator to produce a midline tissue dose rate of 0·25 Gy/min. The total dose of steroid given to each patient was summated and included both pre- and post-transplant treatment. Steroid dose was assessed as total number of weeks of therapy irrespective of the dose or relative potency of the steroid used.

### OPHTHALMIC EXAMINATION

This was undertaken by a single observer (LCB) and included best corrected Snellen visual acuity, assessment of precorneal tear film, extent of conjunctival and corneal rose Bengal staining, and a Schirmer's test.[12] The crystalline lens and fundus were examined following dilatation of the pupils with 1% tropicamide. The degree of cataract was graded in accordance with the Oxford Clinical Cataract Classification and Grading System.[13] Keratoconjunctivitis sicca (KCS) was diagnosed if there were poor tear films, superficial punctate staining of the conjunctiva with rose Bengal, and a Schirmer's test of less than 6 mm/5 minutes. The punctate staining was graded as absent (0), mild (1),

*Table 1 Composition of the treatment groups by diagnosis*

| | *ALL* | *AML* | *CML* | *Lymphoma* |
|---|---|---|---|---|
| Group 1 | 0 | 1 | 0 | 10 |
| Group 2 | 9 | 0 | 0 | 4 |
| Group 3 | 4 | 8 | 5 | 0 |

ALL=acute lymphoblastic leukaemia AML=acute myeloid leukaemia CML=chronic myeloid leukaemia 'Lymphoma' includes both Hodgkin's and non-Hodgkin's lymphomas

*Table 2 Superficial punctate epitheliopathy (SPE) grading distribution for the treatment groups*

| *SPE grade* | *0* | *1* | *2* | *3* |
|---|---|---|---|---|
| Group 1 | 6 | 2 | 3 | 0 |
| Group 2 | 2 | 3 | 3 | 5 |
| Group 3 | 3 | 3 | 6 | 5 |

*Table 3 Total steroid doses and post-transplant review times for treatment groups*

| | *Steroid dose (weeks) Mean (SD)* | | *Review time (months) Mean (SD)* | |
|---|---|---|---|---|
| Group 1 | 25·2 | 8·8 | 23·6 | 13·0 |
| Group 2 | 21·2 | 4·4 | 35·6 | 20 4 |
| Group 3 | 20·9 | 27·5 | 36·0 | 24·5 |

*Table 4 Total steroid doses and post-transplant follow-up times of those with and without cataracts*

| | *Steroid dose (weeks)* | | *Review time (months)* | |
|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* |
| Cataract present | 21·5 | 9·7 | 46·5 | 19·9 |
| Cataract absent | 22·8 | 24·4 | 19·3 | 10 9 |
| Significance (df) | NS | | p<0·0001 | |

moderate (2), or severe (including confluent areas of epithelial loss (3).

### STATISTICAL ANALYSIS

Comparisons of mean steroid doses and post-transplant review times were made between the three treatment groups and between those patients with and without cataract. Single-tailed Student's *t* test analysis ($p<0·05$) was used to evaluate the effects of increasing post-transplant review time and total steroid dose on the likelihood of cataract formation.

## Results

### GROUP 1 (AUTOLOGOUS BMT WITHOUT IRRADIATION)

Cataracts were observed in one of the 11 patients in this group. This patient, who was examined at 34 months post-BMT, had grade I posterior subcapsular cataracts. The remaining 10 patients did not have cataracts when examined at six to 45 months post-BMT. None of the patients had dry eyes, though superficial punctate epitheliopathy affecting the inferior bulbar conjunctiva and inferior cornea, was observed in five patients (Table 2).

### GROUP 2 (AUTOLOGOUS BMT WITH IRRADIATION)

Seven of the 13 patients in this group had cataract (including six of the nine patients with acute lymphoblastic leukaemia) at 36–62 months post-BMT. All cataracts were posterior subcapsular of various grades: I (one patient), II (three patients), IV (one patient), and V (two patients). These last two were sufficiently visually handicapped to require bilateral cataract extractions. The remaining six patients, examined at 6–23 months post-BMT, did not have cataracts. No patients in this group had dry eyes. However, superficial punctate epitheliopathy of the inferior bulbar conjunctiva and inferior cornea was seen in 11 patients (Table 2).

### GROUP 3 (ALLOGENEIC BMT WITH IRRADIATION)

Twelve of the 17 patients in this group had cataracts when examined at seven to 84 months post-BMT. All cataracts were posterior subcapsular cataracts of various grades: I (seven patients), II (two patients), and III (three patients). One patient had grade I cataracts at seven months after transplant, having received a total of 16 g of methylprednisolone during treatment for adult respiratory distress syndrome following BMT. One of those with grade III posterior subcapsular cataracts required cataract extraction. The remaining five patients showed no signs of lens opacity at seven to 33 months post-transplant.

Acute GVHD developed in 12 of these patients, seven of whom had clinical signs of keratoconjunctivitis sicca. Two of these patients had superior tarsal scarring. Chronic GVHD developed in 9 patients and was preceded by acute GVHD in all but one case. Five of these nine had clinical signs of keratoconjunctivitis sicca, but no serious sequelae of dry eyes were observed in any of these patients. Dry eyes were also found in one patient who did not have preceding GVHD. Superficial punctate epitheliopathy affecting the inferior bulbar conjunctiva and inferior cornea were observed in 14 cases (Table 2), and tended to be more severe in patients with GVHD.

There were insufficient data to allow statistical comparisons of steroid doses and post-transplant review times between the three groups. Mean steroid doses for the three groups were broadly similar, as were mean post-transplant review times for autologous and allogeneic grafts receiving TBI (Table 3). However, review times for group 3 were somewhat shorter than for the other groups.

Overall, the incidence of cataracts was 63% (19 of 30) of those patients who received TBI prior to transplantation and 9% (1 of 11) of the non-irradiated patients. There were no significant difference in steroid therapy between those who developed cataracts (including the non-irradiated cataract patient) and those who did not (Table 4). However, post-transplant review times were significantly greater in the former group than in the latter (Table 4).

## Discussion

The association between cataract formation and exposure to ionising radiation was first recognised in the last century.[14] The relationship depends not only on total dose used, but on the rate of exposure, as illustrated by Merriam and Focht,[15] who estimated the minimum dose of radiation required to produce a cataract varied from 2 Gy if given as a single dose to 5·5 Gy if given over longer than three months. However, cataract formation was not observed in some patients receiving as much as 11 Gy.

Similarly, dramatic differences in the incidence and severity of cataract were observed in BMT patients receiving TBI at different rates of exposure.[8] In a large comparative study in Seattle, the reported incidence of cataract was 80% in those receiving single shot TBI (ssTBI) in comparison with 19% for those given fractionated TBI, and was surprisingly no greater than in those given no TBI. More recently Livesey *et al*[10] found that 15 of 18 patients who received ssTBI had cataracts, as compared with only one of 16 who received either fractionated or no TBI. However, no patient in the latter group had been seen at greater than 18 months after transplantation.

Our finding of a 63% incidence of cataracts among those patients receiving fractionated TBI contrasts sharply with previous reports. The mean post-transplant review time of those who developed cataracts was 46·5 months in comparison with only 19·3 months for those who did not. In the Seattle study[8] it was observed that the risk of cataract development increases for the first 30 months after transplantation following fractionated TBI and for 24 months for non-irradiated patients before declining in both cases. Of the 13 patients in our study who received fractionated TBI but did not have cataracts 12 had received their BMT within 30 months of examination. Thus with further follow-up an even greater incidence of cataract might be observed in our irradiated patients. For similar reasons one could argue that the true incidence of cataract among non-irradiated patients may be higher, as only six of the eleven patients in our non-irradiated group had exceeded 24 months after transplantation.

Three additional factors were said by Deeg and colleagues' group[8] to contribute to the development of cataract in these patients: a history of acute or chronic GVHD, steroid usage after day 100 ('chronic usage'), and an initial diagnosis of acute lymphoblastic leukaemia. They could not separate the importance of GVHD from the use of steroids in these patients because the two were so highly associated. They suggested that the high incidence in patients with acute lymphoblastic leukaemia may be related to the high pre-transplant doses of steroids used, a finding confirmed in a subsequent study.[9] Among our patients neither steroid therapy nor the frequency of acute lymphoblastic leukaemia appeared to be significantly different between those who developed cataracts and those who did not (though our patient group is small). There was a strong association between the presence of cataract and a history of GVHD, apparently without the excessive use of steroids in this group (8 of the 12 patients had received less than the mean steroid dose for the 'cataract present' group as a whole).

In theory the higher incidence of cataract observed in our study could be explained by differences in steroid administration. Comparisons of steroid therapy between studies are difficult to make, as their measurement is inevitably crude, depending not only on total dose but on duration, type, and relative potency of the particular steroid used in each case. We do not believe that the use of steroids in our group was unusually excessive or at variance with accepted practice, rendering this explanation unlikely.

There were differences both in midline tissue dose rate and fractionation schedule of the TBI administration between our study and the Seattle study[8] which may be significant. All our patients received a midline tissue dose of 0·25 Gy/min in comparison to just 0·04–0·08 Gy/min for theirs. Secondly, our patients were subjected to TBI fractionated over just 1·5–3 days in comparison with 6–7 days for their patients. We believe that these differences in rate of exposure may significantly contribute to the higher incidence of cataract in our study.

Acute GVHD usually develops within the first three-four weeks after BMT. It occurs with varying severity in more than 50% of successfully grafted recipients of allogeneic marrow.[3] Ocular manifestations are reported in 60% of patients.[5] The commonest finding is haemorrhagic pseudomembranous conjunctivitis[6 7] within the first 90 days after transplantation in patients with severe acute GVHD. It is associated with ulceration of the upper tarsal conjunctiva and results in eventual subtarsal scarring. This late sequela of acute GVHD was observed in two of our patients. Dry eyes were reported in 19 of 25 patients in one series,[6] and were observed in seven of 12 of our patients with a history of acute GVHD.

Chronic GVHD usually arises 3–6 months following BMT, affecting 25% to 45% of the survivors of allogeneic transplant.[3] It resembles an autoimmune illness, with scleroderma-like involvement of the skin, chronic liver dysfunction, profound immunodeficiency, and Sjøgren-like manifestations involving salivary and lacrimal glands.[4] Ocular manifestations[5–7] include superficial punctate keratitis, keratoconjunctivitis sicca, cicatricial lagophthalmos, persistent epithelial defects, and sterile and infectious stromal ulceration. The presence of dry eyes in five of nine of our patients with chronic GVHD is consistent with previous reports.

In our study one case of dry eyes was observed in an allogeneic recipient without a history of GVHD. It is known that higher doses of orbital irradiation, in the region of 32–45 Gy, are usually well tolerated but may be associated with dry eyes.[16] One study reports three cases of dry eyes in patients receiving only 12 Gy.[7] Superficial punctate epitheliopathy was an almost universal finding in patients who had undergone TBI and was present, but in less severe form, in non-irradiated patients. It would seem reasonable to ascribe these abnormalities, at least in part, to a toxic effect of TBI on the eye, though its presence in non-irradiated patients suggests that other aspects of the pre-transplant conditioning may also be implicated.

In conclusion, our data suggest that the relationship between irradiation and ocular toxicity is complex, depending not only on total dose but also its rate of administration (that is, midline tissue dose and/or fractionation schedule). Ocular complications may seem trivial in comparison with the serious nature of the systemic disease under treatment, but can assume greater significance in those 55–90% of patients who become long-term survivors of BMT. Careful scheduling of TBI and the sparing use of steroids are of the utmost importance in minimising these complications.

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# FIFTY YEARS AGO

**Sironi (Milan). Electric cataract from industrial and tempestual discharge. (Cataratta elettrica da corrente industriale e da folgore).** *Rass. Ital. d'Ottal.,* September-October, 1939.

Sironi has had the opportunity of seeing cataract due to high tension current and to lightning stroke and comparing the two, he finds the changes identical. He thinks that in lightning stroke the main discharge often misses the person who is affected only by some of the branches, into which the whole breaks up. Thus the potential is reduced to something like that of high power industrial current. It has been said that the occurrence of a cataract shows that the discharge must have passed through the head; the author's cases seem to show that this is not necessary since the burns produced at the point of entrance and exit were on the body and leg. The appearance of the opacity may not follow the accident immediately but may be delayed for many months.

Harold Grimsdale

*Br J Ophthalmol* 1941; 25: 538.

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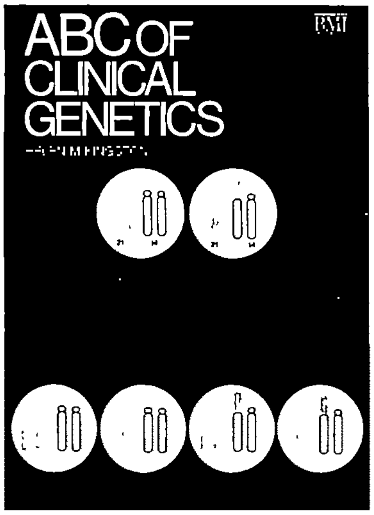

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# Can the pilocarpine phenylephrine provocative test be used to detect covert angle closure?

P K Wishart

**Abstract**

**Mapstone introduced the term 'partial angle closure' to describe how eyes with apparently open angles could be damaged by a covert angle closing mechanism, identifiable by a positive result of the pilocarpine phenylephrine provocative test (PPPT). This paper presents a 10-year follow-up of 68 patients with narrow but open anterior chamber angles who, on the basis of a positive PPPT, underwent peripheral iridectomy (PI) or laser iridotomy LI). In the 42 patients with glaucoma or ocular hypertension the mean intraocular pressure (IOP) was unchanged following iridectomy; 45% of eyes which showed glaucomatous optic disc damage at presentation and 25·6% of ocular hypertensive eyes subsequently required trabeculectomy to achieve IOP control. In 16 patients with no ocular abnormality other than a narrow angle 19 eyes had positive PPPTs and underwent PI. After a 10-year follow-up only one of the 13 untreated fellow eyes developed angle closure glaucoma. As this is usually bilateral, many of the positive tests in this group of patients may therefore have been false positives. This study shows that eyes with narrow angles which had positive PPPT results did not benefit from PI iridectomy or LI and therefore a positive PPPT is not indicative of the presence of an angle closing mechanism.**

To identify partial closure of the anterior chamber angle[1] by a covert angle closing mechanism – an event leading to ocular hypertension and some cases of open angle glaucoma unless relieved by a peripheral iridectomy (PI)[2-4] – Mapstone advocated the use of the pilocarpine phenylephrine provocative test (PPPT).[2-4] The difficulty of predicting the development of angle closure glaucoma (ACG) in an eye with a narrow anterior chamber (AC) angle[5] could be overcome, Mapstone believed, by use of the PPPT, as a positive result identifies the presence of an angle closing mechanism.[6 7] He described the PPPT as more helpful than gonioscopy in the management of eyes with narrow angles,[6-9] and an eye with a positive result of the test should, he stated, undergo a PI to relieve the partial angle closure, lower the raised IOP, and prevent further outflow damage.[2-4]

This study reports an average 10-year follow-up of asymptomatic patients with shallow anterior chambers, narrow but open angles, and raised IOP who underwent a PI or LI when a positive result to the PPPT was taken as an indication that partial angle-closure was present. Follow-up of a group of patients with otherwise normal eyes but with narrow angles who had positive PPPTs and underwent PI is also presented.

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## Patients and methods

Between 1975 and 1986 asymptomatic patients with narrow angles (angle width van Herick grade 2 or less[10] and shallow anterior chamber depths (measured by Haag-Streit pachymetry) with or without glaucomatous optic disc damage attending the Glaucoma Unit at St Paul's Eye Hospital underwent a PPPT to detect if covert angle closure was present. The IOP was above 21 mm Hg in most of them. In all cases presentation was due to the incidental finding of a narrow angle and/or raised IOP and/or glaucomatous disc damage. In no case was there a history suggestive of a previous attack of acute or subacute ACG.

A positive result was taken as a rise of 8 mm Hg in association with a closed angle. Mapstone did not rely on gonioscopy to show if angle closure was present during a PPPT, but assessed this by examining the four quadrants of the eye by van Herick and Shaffer's method[10] to detect peripheral iridocorneal contact.[6] If positive, a PI or LI was performed. If the PPPT gave a negative result, the patient was followed up and treated medically, with repetition of the PPPT at yearly intervals.

Follow-up examination included repeat measurement of the axial AC depth, measurement of the IOP by Goldmann applanation tonometry, stereoscopic optic disc examination performed with the slit-lamp biomicroscope, and Zeiss four-mirror indentation gonioscopy. Visual field analysis was performed with the Friedmann and, later, with the Humphrey visual field analyser to confirm glaucomatous visual field loss when the patient's vision permitted.

## Results

One hundred and thirty-six patients with narrow angles, belonging to one of three groups on clinical grounds, underwent PPP testing:

A. *Glaucomatous.* Patients with glaucomatous optic disc cupping in one or both eyes, raised IOP, and narrow angles.

B. *Ocular hypertension.* Patients with raised IOP, normal optic discs, and narrow angles.

C. *Normals.* Patients with normal IOP, normal optic discs, and narrow angles.

Nine patients were lost to follow-up or had died by 1987, and they were therefore excluded from the study.

Table 1 shows the number of patients and eyes with positive PPPT results and the average age and length of follow-up. Table 2 shows the mean IOP at presentation, and mean anterior chamber

*Table 1 Number of patients and number of eyes with positive PPPTs. Age of patients in years at presentation with years of follow-up in each group – mean (with standard deviation)*

| *Group* | *Patients* | *No eyes +ve PPPT* | *Age (SD)* | *Follow-up years (SD)* |
|---|---|---|---|---|
| A | 20 | 30 | 66·2 (11·0) | 11 95 (3·07) |
| B | 32 | 43 | 63·45 (8·13) | 8 94 (2·96) |
| C | 16 | 19 | 61·38 (8·82) | 10·0 (2·66) |

*Table 2 Intraocular pressure at presentation, and axial anterior chamber depth of eyes with positive PPPTs in each group – mean (standard deviation)*

| *Group* | *ACD, mm (SD)* | *IOP, mm Hg (SD)* |
|---|---|---|
| A | 2·14 (0·29) | 34·2 (11·1) |
| B | 1·96 (0 25) | 28·2 (4 4) |
| C | 2 03 (0·55) | 18 29 (2·0) |

depth in the three groups. There was no difference (within the error of method) between the AC depths at the time of presentation and the follow-up measurements which appear in Table 2. In 10 eyes (9·5%) there was no record of the AC depth. The results are given as mean with standard deviation (SD).

### GROUP A: GLAUCOMATOUS

Twenty patients with glaucomatous damage to one or both optic discs, raised IOP, narrow angles, and shallow anterior chambers had positive PPPT results in one or both eyes. Of the 20 patients (40 eyes) 10 were affected bilaterally and 10 unilaterally. The excluded eyes comprise eight eyes with negative PPPT results and two eyes which had positive PPPT results but were normotensive with normal optic discs.

Thirty eyes had glaucomatous disc damage, raised IOP, a narrow anterior chamber angle, and visual field loss on Friedmann field analysis. As a consequence of a positive result to the PPPT these eyes underwent peripheral iridectomy.

The mean IOP at presentation was 34·2 (SD 11·1) mm Hg and had been reduced to 23·2 (SD 6·9) mm Hg with medical treatment immediately prior to PI. The mean IOP at approximately two months after iridectomy, was 28·8 (SD 5·59) mm Hg.

Despite the PI, the IOP was only lowered in one eye postoperatively. Thirteen (45%) of the remaining 29 eyes in this group ultimately required trabeculectomy to lower the IOP, the others requiring the same or increased medical treatment postoperatively as preoperatively. Thirteen eyes developed cataracts and 12 underwent extracapsular cataract extraction and lens implant (ECCE+IOL). Gonioscopy during follow-up showed open angles. Visual loss due to glaucomatous disc damage was marked in 18 patients, and only one patient (two eyes) retained a visual acuity (VA) of 6/9 with only moderate damage to the visual field. In 15 eyes the final visual acuity was between no light perception and 6/24 owing to glaucomatous damage to central vision.

### GROUP B: OCULAR HYPERTENSION

Ninety patients with ocular hypertension and narrow anterior chamber angles underwent PPP testing. Fifty-eight had negative PPPT results in both eyes, and therefore the outcome in them is not included in this study but has been presented elsewhere.[11] The remaining 32 patients (64 eyes) with positive PPPT results are presented here. All eyes in this group had a recorded pretreatment IOP of at least 23 mm Hg in one or both eyes and normal optic discs. One eye was thought to have peripheral anterior synechiae of the angle, but postoperative gonioscopy did not confirm this finding. Of the 32 patients with positive PPPT results 11 were positive bilaterally, and 21 unilaterally, giving 43 eyes with positive results. These 43 eyes underwent iridectomy – 33 peripheral iridectomy and 10 argon laser iridotomy.

The mean preoperative IOP was 27·66 (SD 4·18) mm Hg for 39 eyes on no medical treatment and four eyes on treatment with timolol or pilocarpine. The mean postoperative IOP at approximately two months following PI or LI was 28·02 (SD 5·8) mm Hg, with two eyes requiring medication and 41 on no treatment. Four eyes became normotensive after PI with an average fall in IOP of 7 mm Hg, though after five years of follow-up three became hypertensive again. Three others, after iridectomy, had a fall in IOP (average 4 mm Hg), though they remained hypertensive. In the remaining 36 the IOP was not lowered and was treated medically. Gonioscopy showed open angles in all eyes. Eleven eyes (25·6%) subsequently required trabeculectomy for IOP control, and nine developed cataracts requiring ECCE + IOL. Six eyes developed optic disc changes over the follow-up period; three eyes showed glaucomatous optic disc cupping, and three optic discs were damaged by vascular occlusions. Twenty two eyes retained vision of 6/9 or better, five had a reduction of visual acuity due to mild lens opacity, and two due to diabetic maculopathy.

### GROUP C: NORMALS

Sixteen patients (32 eyes) with no detectable abnormality other than an incidental finding of a narrow anterior chamber angle had PPP testing. Fifteen patients had positive PPPT results in one eye, and one patient had a positive result in both. Seventeen eyes therefore underwent peripheral iridectomy after initial presentation. The fellow eye in each group was followed up in the Glaucoma Unit with repeat PPP testing. Two fellow eyes later became positive to PPPT and underwent laser iridotomy. The fellow eye in one patient, despite negative PPPT results, spontaneously developed an acute attack of angle closure glaucoma. The anterior chamber depths in this patient were 1·1 mm and 1·3 mm, and the initial PPPT on the first eye induced an attack of acute angle closure glaucoma (ACG). In the remaining 12 patients the 12 fellow eyes retained open anterior chamber angles without pathology and with no signs or symptoms of angle closure glaucoma after an average 10-year follow-up. Four of the initially normotensive eyes that underwent PI later developed a raised IOP but retained normal optic discs. By the end of the follow-up period eight eyes had developed dense cataracts and four underwent ECCE+IOL.

*Table 3 Results of surgery (PI/LI) on eyes in groups A, B, C – mean IOP in mm Hg (SD)*

| | *Group A* | *Group B* | *Group C* |
|---|---|---|---|
| Mean IOP pre-PI | 23·2 (6·9) | 27·66 (4·18) | 18·29 (2·0) |
| Mean IOP post-PI | 28·8 (5·59) | 28·02 (5·8) | 19·47 (3·35) |
| Required trabeculectomy | 45% | 25·6% | Nil |
| Developed cataract | 43% | 21% | 36·8% |

Seven of these cataracts developed in eyes that had undergone peripheral iridectomy, and one untreated eye developed a cataract.

Table 3 summarises the results of the three groups undergoing surgery.

## Discussion

Acute, subacute, and chronic angle closure glaucoma are precise and well established terms for varieties of pupillary block glaucoma diagnosed by a combination of history and clinical examination including gonioscopy.[12–15] Mapstone has introduced the term partial angle closure[1] to describe a type of ACG, identifiable by a PPPT and responding to a peripheral iridectomy,[3 4] which can occur without symptoms in eyes with apparently open angles.

Clinical experience has shown peripheral iridectomy to be a highly successful treatment for acute ACG, with, on average, 70% of eyes with acute ACG achieving normal IOP following PI alone.[16–20]. Similarly, eyes with subacute ACG respond to a PI.[19 21] or LI[22] but often in addition require topical medication.

Studies of patients with medically uncontrolled chronic angle closure glaucoma have shown that even where field loss and significant synechial closure of the anterior chamber angle is present approximately 70% of eyes will achieve satisfactory control with PI of LI and topical medication.[19–24] In eyes suffering from chronic angle closure glaucoma without field loss and without peripheral anterior synechiae in the angle PI is strikingly successful, with 66% of such eyes in Gelber and Anderson's study,[23] 69% in Playfair and Watson's series,[21] and 78% in Forbes's study[14] cured by PI alone.

In contrast to the marked success of peripheral iridectomy in the treatment of angle closure glaucoma in the above studies, it failed to help the patients in groups A and B of this study, in whom a positive PPPT result was said to have identified partial angle closure as the underlying cause of their raised IOP. Only one of the eyes in group A seemed to benefit from PI, and 50% of eyes in this group suffered severe progressive visual loss from glaucoma. 45% of eyes in group A ultimately required trabeculectomy. The outcome of the eyes in group B which were diagnosed as having partial angle closure showed that after PI only four (9·3%) became normotensive off medication, and this fall was not sustained in three eyes. Had the eyes in group B been suffering from chronic ACG, they would have belonged to the group with the most favourable prognosis, having neither field loss nor PAS, and at least 66% would be expected to become normotensive following PI alone.[14 21 23] 25·6% of eyes in group B ultimately required trabeculectomy to achieve IOP control.

In the normotensive patients in group C the need for an iridectomy cannot be judged postoperatively on the basis of a change in IOP. However, as angle closure glaucoma is usually a bilateral disease, occurring in some 70% of fellow eyes,[25–28] the fate of the fellow eyes in group C can give some indication as to whether this group was genuinely suffering from covert ACG. Only one (8%) of the fellow eyes in this group without an iridectomy developed ACG, and this was in a high risk eye with an exceptionally shallow anterior chamber depth (1·1 mm).[25] The other fellow eyes in this group showed no signs or symptoms of ACG and retained narrow though open angles throughout the 10-year follow-up.

The only indication that the patients in this study were suffering from angle closure was a positive PPPT result, which Mapstone believed identified partial angle closure or a covert angle closing mechanism.[1–4] The failure of PI to benefit the eyes in groups A and B leads one to conclude that the patients in groups A and B could not have been suffering from ACG. Similarly, follow-up of the patients in group C shows that, with the exception of one eye, this group was not at high risk of angle closure glaucoma.

Mapstone's PPPT relied on van Herick and Shaffer's method[10] of estimation of the depth of the peripheral anterior chamber to determine when the angle was closed[1 3 6] and not on gonioscopy, which he considered provided only a subjective assessment of narrowness of the anterior chamber angle.[1 4 6 7]. This study has shown that a large number of eyes with narrow angles developed an 8 mm Hg rise in IOP and a closed angle assessed by van Herick and Shaffer's method – a positive result – on PPP testing. As follow-up has not shown these eyes to have been suffering from ACG, it appears likely that the unphysiological maximal sympathetic and parasympathetic forces occurring simultaneously during the PPPT resulted in the creation of a pupillary block force that led to shallowing of the periphery of the anterior chamber and a rise of pressure. As 100% of eyes in group A with glaucomatous optic discs had positive results to PPP testing and in group B only 24% of eyes (43 of 180 tested) gave positive test results, this may be an indication that an already damaged outflow cannot cope with the alteration in fluid dynamics occurring in an eye during a PPPT. This confirms the findings of a recent study which showed that eyes with a history of subacute angle closure glaucoma were 10 times as likely to have a positive PPPT result if they showed optic disc damage than if the optic disc was normal.[17]

It is evident from the results of this study that an eye with a narrow angle can develop an 8 mm Hg rise in IOP and peripheral iridocorneal contact when subjected to a PPPT yet not be suffering from, or at risk of, angle closure glaucoma. If an eye with a narrow angle, raised IOP, and glaucomatous optic disc damage undergoes a PPPT, a positive result is almost inevitable, irrespective of the aetiology of the glaucoma. The belief that the PPPT detects angle closure glaucoma is therefore erroneous, and the evidence that a positive PPPT has identified an otherwise undescribed form of angle closure –

partial angle closure – is not substantiated. Use of the PPPT is therefore not recommended in clinical practice.

I would like to thank Mrs C Owen for technical and administrative help

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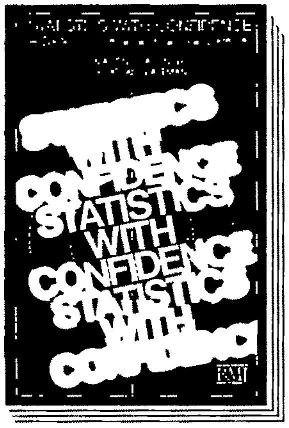

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*British Journal of Ophthalmology*, 1991, 75, 619–621

CASE REPORTS

# Persistent superior oblique paresis as a manifestation of familial periodic cerebellar ataxia

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## Abstract

**A brother and sister complained of persistent diplopia due to superior oblique palsies. The cause of their symptoms became apparent when they were diagnosed as having familial periodic cerebellar ataxia (FPCA), a rare autosomal dominant condition. Oral acetazolamide (250 mg twice daily) not only prevented all the periodic symptoms but also relieved their diplopia, which had been present between attacks.**

## Case reports

### PATIENT A

Now aged 22 years, patient A, male, began at the age of 10 to have 'episodes of giddiness' about once a week, usually while taking exercise. The episodes would last about 10 minutes and, because he became unsteady, forced him to sit down. On the basis of minor electroencephalographic (EEG) abnormalities he was believed to have 'vertiginous epilepsy and was treated with anticonvulsants, but these were unhelpful and were withdrawn. At 16 he developed diplopia and was referred to an ophthalmologist. Examination revealed visual acuities of 6/6 in the right eye and 6/5 in the left. No field defects were present, and there was no significant astigmatic error. His head was tilted and turned to the left, and a right superior oblique palsy was apparent on testing his eye movements. This was confirmed on a Hess chart (Fig 1). There were no abnormal physical signs and in particular no cerebellar deficit.

### PATIENT B

Now aged 19 years, patient B, female, had been healthy as a child except for a slight delay in speech development. At the age of 10 she began to get 'attacks' that occurred up to five times a week and might last several hours, consisting of intermittent diplopia, true vertigo, and unsteadiness of gait. The attacks were precipitated by exertion, emotional stress, and menstruation and were always relieved by sleep. On the basis of

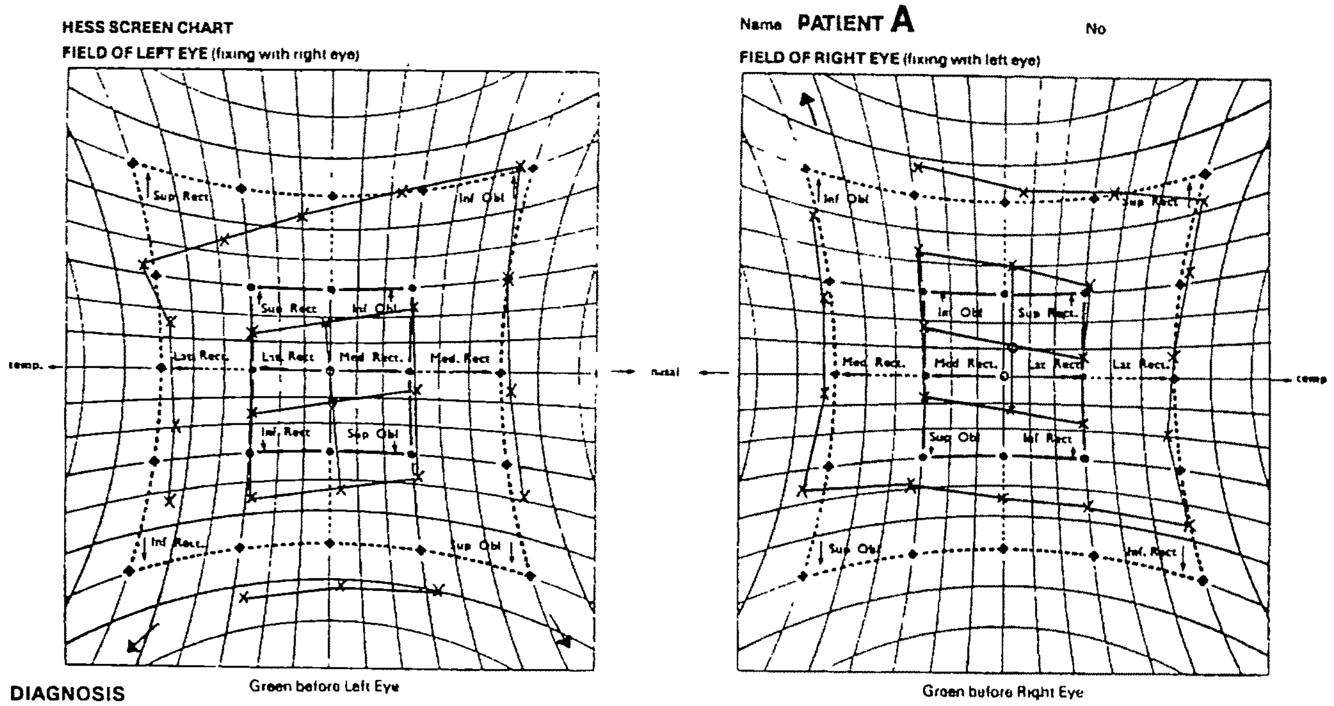

*Figure 1 Hess chart demonstrating right superior oblique palsy in patient A. Ipsilateral (right) inferior oblique overaction and superior rectus underaction with contralateral (left) superior rectus underaction and inferior rectus overaction are also present, which suggests that the palsies are long standing.*

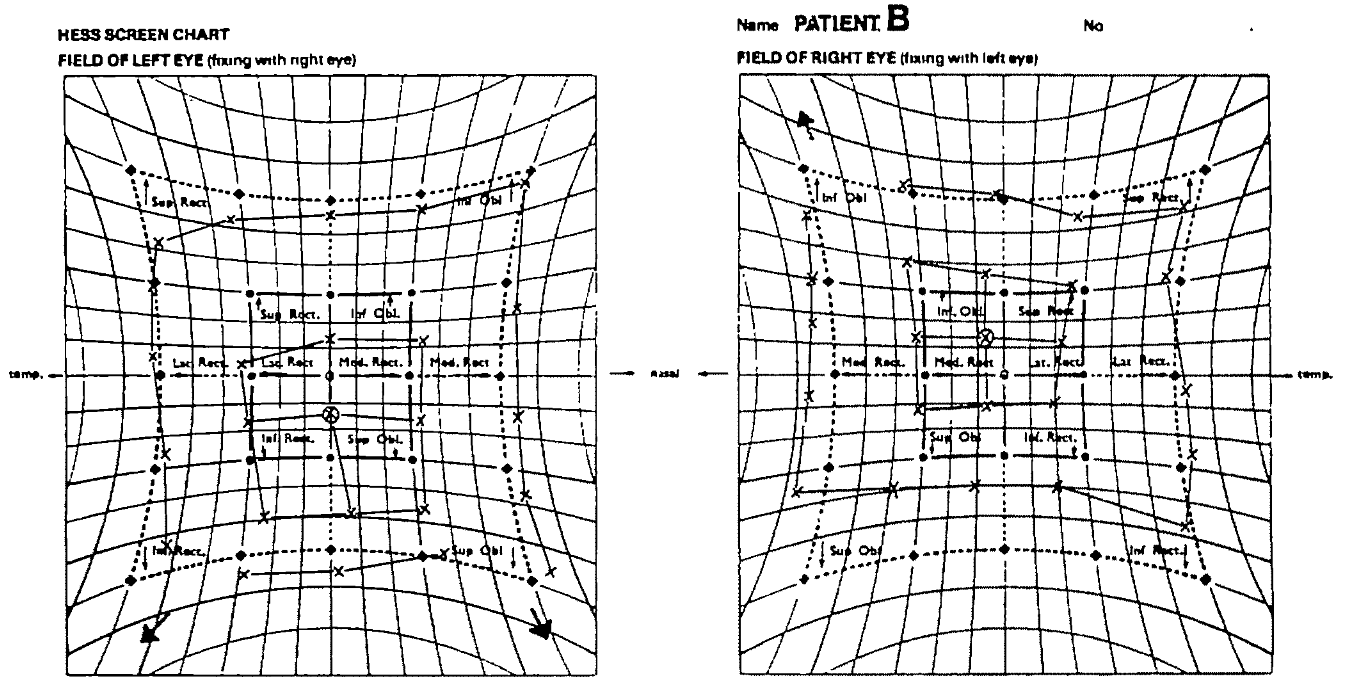

*Figure 2 Hess chart demonstrating right superior oblique palsy in patient B Details as for Figure 1.*

minor EEG irregularities, she was prescribed anticonvulsants, but these merely exacerbated her diplopia and increased the severity of the attacks and were eventually withdrawn. At the age of 13 she was referred for an ophthalmic opinion because of persistent diplopia. On examination her corrected visual acuities were 6/9 bilaterally. She had normal visual fields and no significant astigmatic errors. There was a right superior oblique palsy which was recorded on a Hess chart (Fig 2). Her head was tilted and rotated to the left, but no other abnormalities were evident on general physical examination, and there was no cerebellar deficit.

The father of both patients had experienced similar 'giddy spells' since childhood. These episodes recurred weekly, lasted about 20 minutes, and consisted of slurred speech and incoordination of the lower limbs. He was unable to stand during an attack. Examination, between episodes showed ocular dysmetria, a scanning dysarthria, and transient first degree nystagmus on looking to the right. He had never complained of diplopia, and there was no evidence of an extraocular muscle palsy. No other members of the family appeared to be affected.

*Table Types of nystagmus found, between attacks, in familial periodic cerebellar ataxia*

*(A) In primary position of gaze*
(i) Downbeat
(ii) Oblique downbeat
(iii) Rotary

*(B) Gaze evoked*
(i) Intermittent 1° horizontal
(ii) Persistent 1° horizontal
(iii) Asymmetric horizontal (with increased amplitude of the jerks in the abducting eye).
(iv) Downbeat
(v) Upbeat
(vi) Combinations of horizontal and vertical

INVESTIGATIONS
Both patients underwent identical investigations, which included a cerebral CT scan, pure tone audiometry, optokinetic nystagmus, blood ammonia and amino acid assays, a full blood count, erythrocyte sedimentation rate, liver function tests, urea and electrolytes, blood sugar, vitamin $B_{12}$ and red cell folate levels, mid stream urine tests, and urinary amino acid assays; the results were all normal. Repeat EEGs were normal in both patients.

The family's intermittent symptoms suggested a diagnosis of familial periodic cerebellar ataxia. Treatment with oral acetazolamide (250 mg twice daily) abolished all their attacks, and Hess chart examinations confirmed that the superior oblique palsies had resolved. The effectiveness of acetazolamide has been maintained, without a single relapse, for over a year. Their diplopia has not recurred.

## Discussion

Familial periodic cerebellar ataxia was first described by Parker in 1946.[1] Since then several families have been described[2-13] in which disabling attacks of dysarthria, limb ataxia, and dysequilibrium occur. In the majority of these families the attacks have lasted from 10 minutes to 6 hours, were inherited as an autosomal dominant characteristic, and were preventable by oral acetazolamide. Between ataxic episodes the patients were usually asymptomatic and on examination were completely normal or had mild cerebellar signs, including the following ocular motility disorders: bidirectional square wave jerks on attempted fixation, broken pursuit movements, dysmetric saccades, and the types of nystagmus documented in the Table. In one very atypical case, a 3-year-old with craniofacial dysmorphism[12] (kindred II, patient IV-35), ptosis was observed, and in one other case[5] (case 3) decreased upgaze was reported.

Our observation of persistent right superior oblique palsies in siblings with FPCA is unique, and illustrates the heterogeneity of the eye signs in this condition. The responsiveness of their diplopia to acetazolamide, which also abolished their attacks, suggests that the palsies were not coincidental but the direct result of the underlying defect in FPCA. Evidently this disease can affect systems outside the cerebellum and its connections, in our cases involving the IVth nerve or superior oblique musculature. This suggestion is supported by Trillet *et al*,[11] who observed abnormalities in the visual (longer lag period) and somataesthetic (slowed conduction rate in the medial lemniscus) evoked potentials of their patients.

FPCA is easily misdiagnosed or unrecognised and may be more frequent than is generally appreciated.[12] It appears capable of causing a variety of ocular manifestations which can persist between attacks. Once recognised it is treatable, responding impressively to maintainence oral acetazolamide, 250 mg twice daily. This diagnosis should be considered in patients presenting with intermittent ataxia or vertigo.

We thank Professor A E Harding for her advice and Elizabeth Chitty for her help in preparing the manuscript.

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# Tolerance of the eye for implanted cilia

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## Abstract

**Retained cilia in the eye following injury are rare. There are reports of long term tolerance to cilia in the anterior chamber but no information about the effect on the corneal endothelium. A 31-year-old man was seen with a 19-year history of a retained eyelash embedded in a corneal scar and extending across the anterior chamber to the chamber angle. The follicle was absent. There was no cellular inflammatory reaction, and the eye otherwise appeared normal on slit-lamp examination with normal vision. However, there was the appearance of an encrusted deposit on the surface of the lash and a markedly lowered endothelial cell count of 750 cells/mm$^2$ compared with the fellow eye. The lash was not removed.**

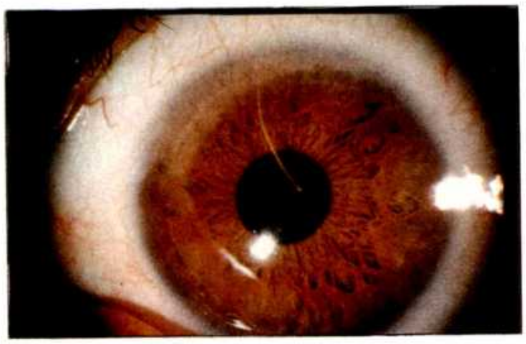

*Figure 1 Slit-lamp biomicroscopy of the left eye showing a pale slightly tapering elongated foreign body consistent with an eyelash lying in the anterior chamber extending from a scar close to the visual axis to the angle superiorly. The eye is quiet.*

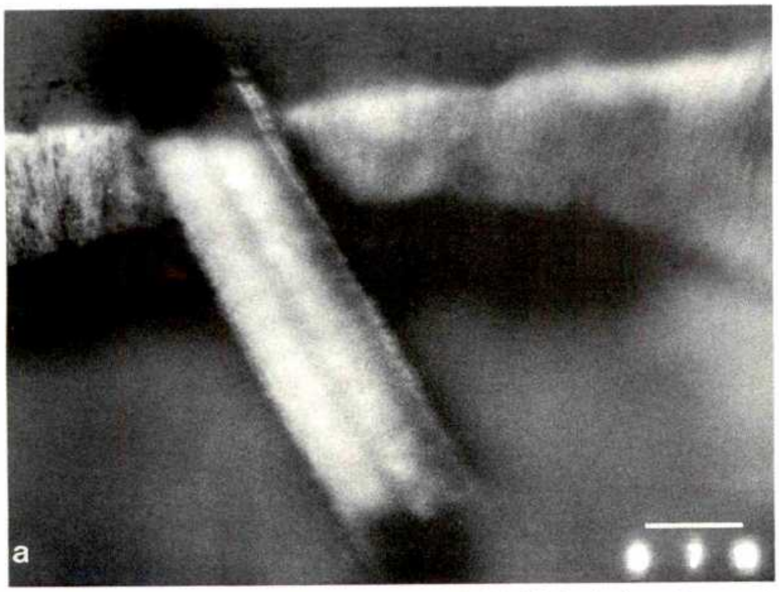

*Figure 2 Specular microscopy of left eye showing a cylindrical foreign body running across the anterior chamber with an irregular encrusted surface consistent with deposition of material upon an eyelash. Detail of the iris is seen behind the lash. (Bar=100 μm.)*

Reports of an eyelash in the eye are uncommon,[1] though there are reports of remarkably long term tolerance of the eye to cilia.[2] To our knowledge there are no reports of the effect of retained cilia on the corneal endothelium

## Case report

A 31-year-old man from Luxor, Egypt, presented in July 1990 complaining of long-standing, intermittent, bilateral ocular irritation. He stated that, when aged 12 years, four or five days after an injury to the left eye with a fountain pen tip he was admitted to Luxor Hospital, where one eyelash was removed but another left in the eye. Following intensive antibiotic drops and one outpatient review he had no further trouble until the recent ocular irritation.

On examination vision was right eye 6/6 with $-1{\cdot}50\times5°$ and left eye 6/6 with $-1{\cdot}25\times10°$. Both eyes showed mild superior corneal pannus and subtarsal scarring. There was a small old full thickness scar in the mid cornea of the left eye, with a pale, elongated, tapering foreign body extending from the upper margin of this scar across to the angle of the anterior chamber at 11 o'clock (Fig 1). The anterior chamber was quiet, with no inflammatory reaction, and both eyes were otherwise normal. Gonioscopy showed the tapered tip of the foreign body lying on the trabecular meshwork with a little surrounding pigmentation.

Specular microscopy showed the oval cross section of a foreign body consistent with an eyelash arising from the upper margin of the old corneal scar (Figs 2, 3). The surface had a slightly irregular encrusted appearance suggesting a cocoon of precipitate (Fig 2). The corneal endothelium showed a marked lowering of endothelial cell count (750 cells/mm$^2$) over the whole endothelial mosaic, with moderate pleomorphism and polymegathism but no signs of active inflammation or oedema (Fig 3). The endothelium in the fellow eye was normal (2700 cells/mm$^2$).

The patient's mild ocular irritation settled with simple topical decongestant drops. No attempt was made to remove the foreign body.

## Discussion

Previous reports of eyelashes retained in the eye include instances of lashes tolerated for a long period with little or no reaction provided the follicle was not included.[1-7] Delayed inflammatory reactions have been reported,[4] and lashes in the vitreous or retina have been tolerated,[8 9] though others have caused serious consequences.[10] As early severe reactions to the presence of a lash have been described,[1 11 12] removal is best in recent cases when the accompanying injury is explored and repaired. How-

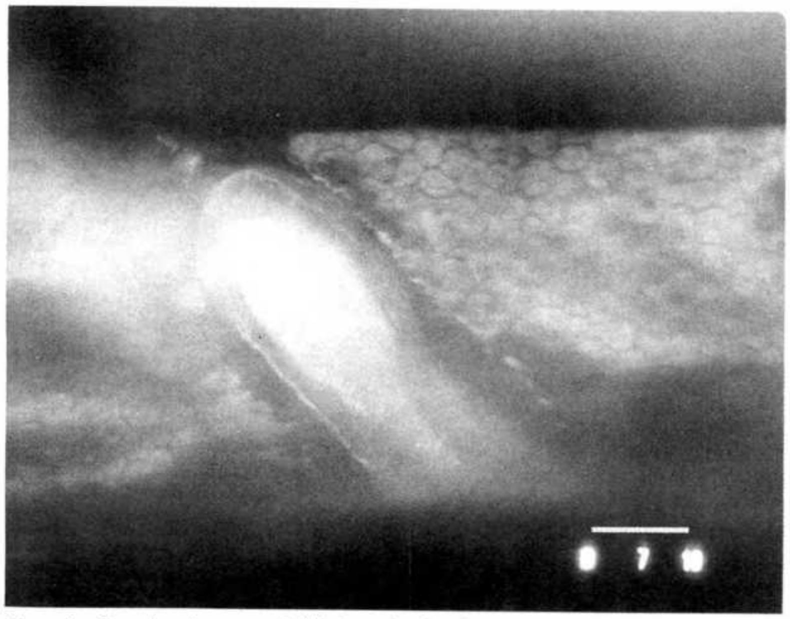

*Figure 3 Specular microscopy of the left eye showing the cross section of a cylindrical foreign body embedded in a corneal scar. The adjacent corneal endothelium shows a lowered endothelial cell count of 750 cells/mm² with moderate pleomorphism and polymegathism. (Bar=100 μm.)*

ever, in long-standing quiescent cases removal may be deferred and the patient observed.

Pallor of the lash has been noted previously.[1 3 4] Under the high magnification of specular microscopy this pale appearance was consistent with an encrusted deposit on the lash, suggesting a very low grade reaction which is probably biochemical rather than cellular.

The endothelial cell count in the present case was much lower than would be expected from a relatively minor penetrating injury. The low count may be due to surgical trauma, but the small wound with only one lash removed makes this unlikely. Alternatively the low endothelial cell count may represent a long-term low grade reaction to the presence of the lash, either an irritant biochemical effect associated with the crusting of the lash or a mechanical effect from its contiguity with the endothelium. No cellular inflammatory response was present.

This case re-emphasises the ability of the eye to tolerate almost indefinitely the presence of an eyelash foreign body with retention of normal visual function provided the lash follicle is not present, but it points to a disproportionate effect on the corneal endothelium which needs to be monitored.

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# Homonymous horizontal sectoranopia: report of four cases

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## Abstract

**Four cases of right homonymous horizontal sectoranopia are described. They were investigated with automatic static perimetry matched in three cases with Goldmann perimetry. In two cases – a wound of lateral sinus, a temporal surgically excised oligodendroglioma – neuroradiological investigations localised the visual pathways lesion to the optic radiations. In two other cases the lesions of vascular origin were less precise. In both of these there were ischaemic phenomena. In one of them the left anterior superficial sylvian territory was involved and in the other the left anterior choroidal artery territory was in question. This visual field pattern, less rare than was previously supposed, seems in some cases to correspond to retrogeniculate and varied topographic lesions.**

Homonymous horizontal sectoranopia is a rare and remarkable visual field defect, described in 1931 by Holmes.[1] Pathological[2] and radiological studies[3-6] have argued for a precise correspondence between this visual field pattern and a lesion of the contralateral geniculate nucleus (LGN). However, there are arguments against this exclusive anatomical correlation. Homonymous horizontal sectoranopia has also been described in lesions of the optic radiations[7-10] and of the occipital lobe.[1 11]

We have observed four new cases over the last three years, none of them showing a characteristic LGN alteration at least on CT scan or magnetic resonance imaging (MRI). We believe that this visual field pattern is less rare than previously thought.[10]

## Patients

During 1987–90 we examined seven patients with a homonymous horizontal sectoranopia. We selected four of them who had a neuroradiological investigation performed (CT scan and/or MRI). An automatic static perimetry (AP) was undertaken in all cases and was compared in three with the Goldmann chart. The AP was mapped on the Vision Monitor (Metrovision) with a standardised programme. The static protocol included a suprathreshold strategy (4 dB above the theoretical luminance threshold) for the 94 points tested in the central 30° and a laminal strategy for the foveolar point.[12] Eight additional measurements were used to chart the blind spot contour. In two cases a study of the nerve fibre layer was carried out by a technique previously described.[13]

## Case reports

### CASE 1

We examined a 66-year-old hypertensive woman six months after she suffered partially regressive Wernicke's aphasia. A Doppler investigation showed 30% stenosis of both carotid arteries. The visual acuity was right eye 20/25, left eye 20/20. The fundi were normal. Static automatic perimetry disclosed a small, right, horizontal, incongruous, homonymous scotoma, triangular in shape (Fig 1). A CT scan at the time of the stroke showed an ischaemic anomaly limited to the left anterior superficial sylvian territory (Fig 2).

### CASE 2

A 59-year-old man suddenly complained of severe headache associated with visual trouble.

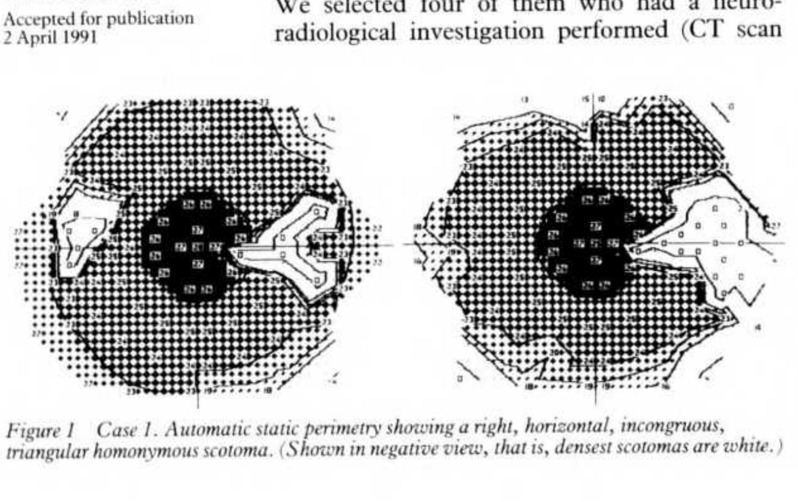

*Figure 1 Case 1. Automatic static perimetry showing a right, horizontal, incongruous, triangular homonymous scotoma. (Shown in negative view, that is, densest scotomas are white.)*

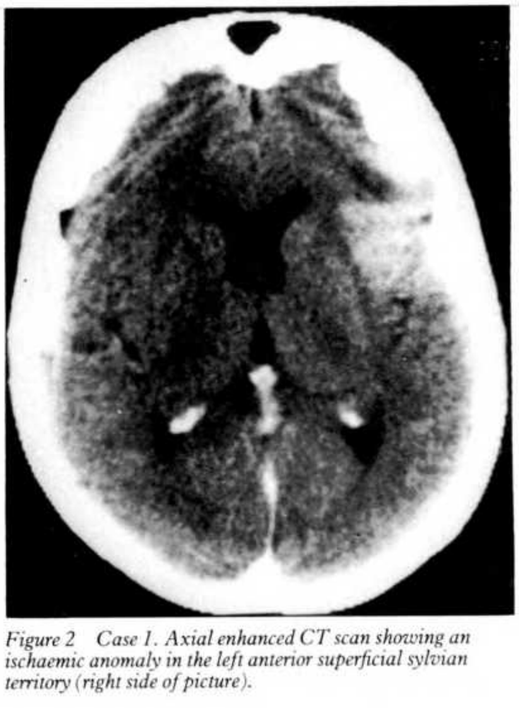

*Figure 2 Case 1. Axial enhanced CT scan showing an ischaemic anomaly in the left anterior superficial sylvian territory (right side of picture).*

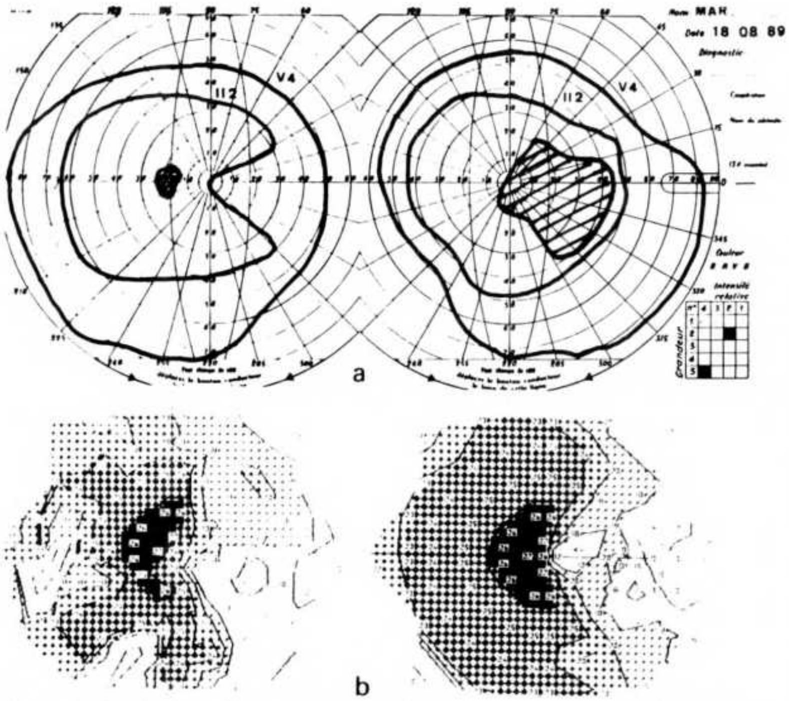

*Figure 3 Case 2. Visual field chart showing right homonymous sectoranopia. a: Goldmann perimetry. b: Automated perimetry.*

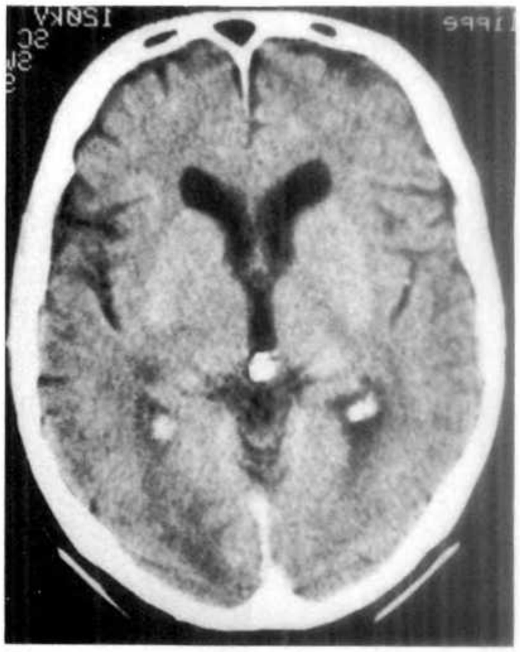

*Figure 4 Case 2. Axial CT scan showing ill defined hypodensity in the left anterior choroidal artery territory (right side of picture).*

He was responsible for a driving collision and later noticed disabilities with reading. In the past he had suffered from asthma, Raynaud's syndrome, and polyarteritis nodosa. His visual acuity was 20/30 in both eyes. A perimetric study (Fig 3) disclosed a right incongruous homonymous horizontal sectoranopia by both techniques (Goldmann and AP). On automatic perimetry the defect was larger but less characteristic of a sectoranopia. The fundus was normal. The CT scan showed a sacciform aneurysm of the supraclinoid part of the left internal carotid and a subcortical hypodensity suggesting an infarction limited to the territory of the anterior choroidal artery (Fig 4).

CASE 3

A 28-year-old woman complained of nausea and diplopia for a few days. She had a bilateral VI nerve paresis and papilloedema. A diagnosis of 'benign intracranial hypertension' was made. She was obese and had been taking a low-progesterone contraceptive pill since her last delivery five months previously. She had been surgically treated for a traumatic wound of the left lateral sinus when she was 5 years old. The opening pressure of the CSF reached 30 cm $H_2O$ and a cytochemical analysis gave normal results. Her vision was normal (20/20) in both eyes. She had a florid papilloedema, with a marked dilatation of the papillary capillaries. The visual field (Goldmann and automatic static perimetry) (Fig 5a) disclosed an enlargement of the blind spot and a right incongruous homonymous horizontal sectoranopia. The size of the sectoranopia decreased with improvement of the intracranial hypertension. Four months later (Fig 5b) the typical visual field defect remained more apparent on automated perimetry than on the Goldmann chart. The retinal nerve fibre layer showed no abnormal features. On CT scan (Fig 6) the ventricles were small; a left parenchymatous temporal hypodensity with a retractile aspect was observed and considered to be a scar from craniocerebral trauma in childhood. The left lateral sinus was not opacified at the arteriography.

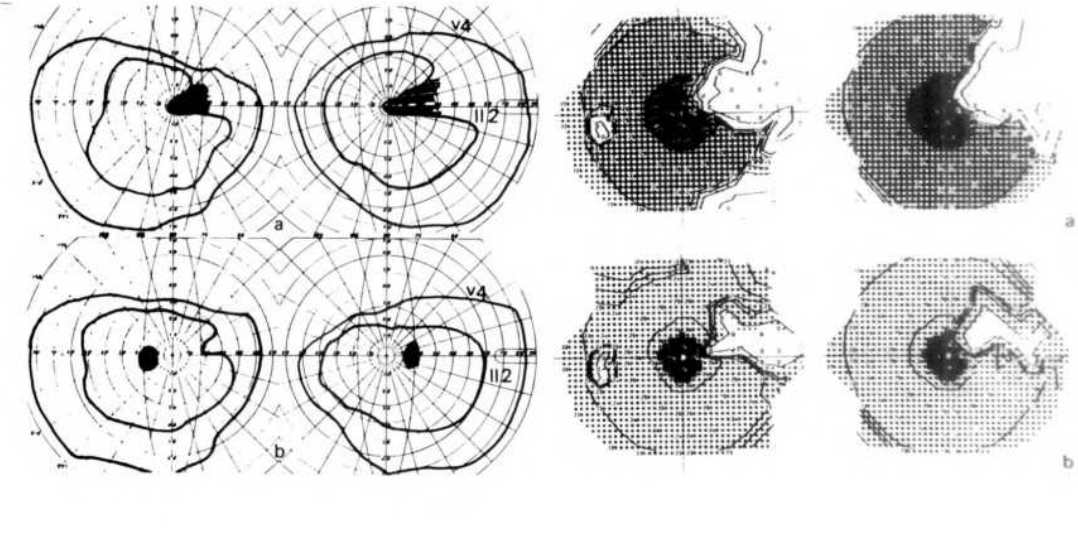

*Figure 5 Case 3. Visual field, right homonymous sectoranopia. a: Top left Goldmann chart, top right automatic perimetry. b: Four months later, after resolution of both the papilloedema and intracranial hypertension.*

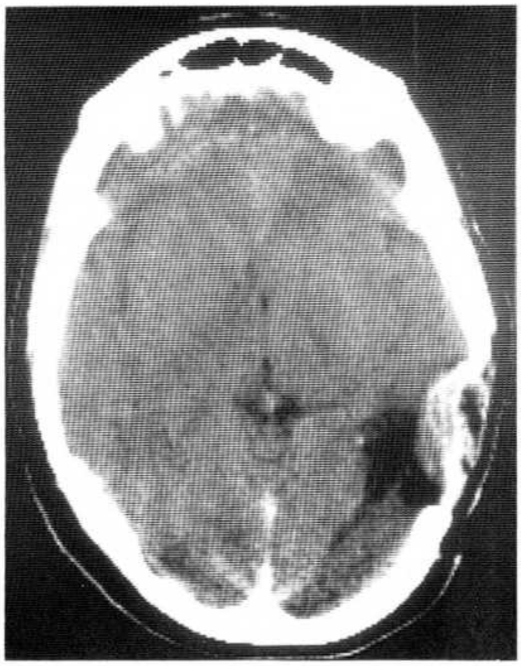

*Figure 6 Case 3. Enhanced CT scan showing a left parenchymatous temporal scar (right side of picture).*

### CASE 4

A 25-year-old man had a surgical resection of a left temporal lobe oligodendroglioma. He had developed epilepsy at the age of 4, with both grand mal seizures and absences. The ophthalmological investigation was undertaken after surgery when he first complained of visual disabilities. The visual acuity was normal (20/20) in both eyes. The visual field showed by both techniques (Goldmann and AP) a right horizontal incongruous homonymous sectoranopia (Fig 7a). On MRI an area of abnormal signal was located in the posterior and inferior part of the left temporal lobe from its most superficial aspect to the occipital horn (Figs 8, 9). Four months later the size of the visual field defect decreased (Fig 7b) and lost its pattern of sectoranopia on Goldmann perimetry. However, the scotoma retained a 'fish-like' aspect on AP. The appearance of the retinal nerve fibre layer was normal.

## Discussion

Homonymous horizontal sectoranopia has been little documented. Since 1978 five papers[4 5 6 10 11] to our knowledge have been published reporting a total of eight cases (Table). Seven cases were investigated by CT scan and one with arteriography alone.[3] The present series of four cases is the largest using modern neuroradiological investigations. All previously reported cases had left homonymous sectoranopia. They corresponded to a right hemispheric lesion of various causes – craniocerebral wound,[7] astrocytoma,[2 5 10] vascular involvement,[6 8 9 11] or arteriovenous malformation.[1 3 5 10]

Our cases had an incongruous right horizontal homonymous sectoranopia in relation to an ischaemic stroke in cases 1 and 2 and to a wound in cases 3 and 4. All of them retained good visual acuity, ranging from 20/30 to 20/20, as observed in previous cases.[2 3 5 9-11] For three of them it was possible to match both techniques of visual field investigation – automatic static perimetry and kinetic perimetry. In general there was a good correspondence between the two methods. However, the defects on Goldmann perimetry looked more congruous than on the AP. The artificial enlargement of the central 30° given by AP is the first explanation. Secondly, the mapping of the blind spot on AP accentuated the asymmetry. In our four cases the visual field pattern was right sided and the visual field defect on the right chart of AP appeared larger than on the left, probably because of the blind spot.

In fact the aspect of sectoranopia in AP is not well known. In the cases previously described[1-11] all the patients but one[6] had only Goldmann perimetry. In our case 2 the defect on AP was more extensive than on Goldmann but less characteristic of sectoranopia. It looked like a classical homonymous hemianopia. This statokinetic dissociation has previously been described in postchiasmal lesions.[14] In the first two cases an ischaemic stroke was responsible for lesions – of the left anterior superficial sylvian territory in the first case and of the anterior choroidal artery territory in the second.

The lesions were ill defined, and anatomical correlations could not be precisely provided,

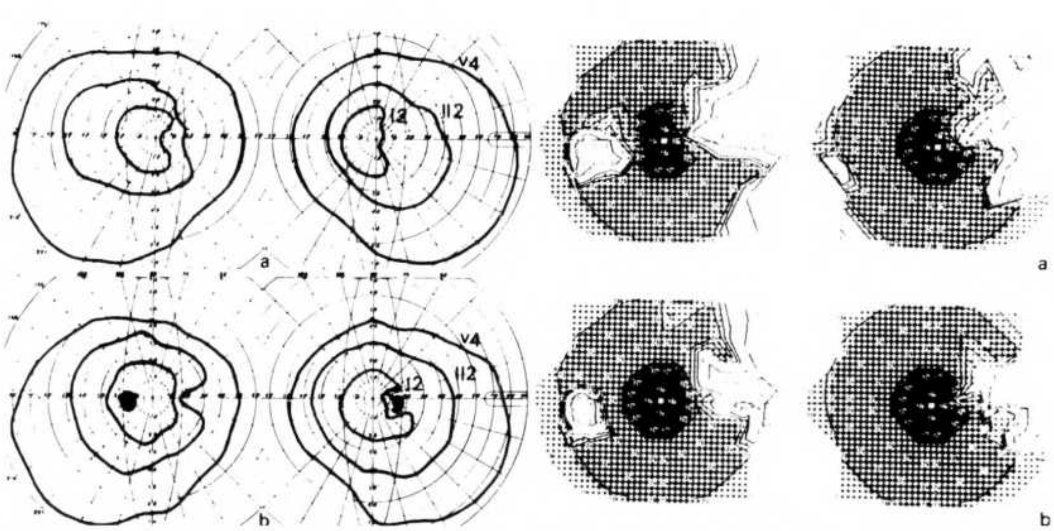

*Figure 7 Case 4. Visual field. Right horizontal homonymous sectoranopia. a: One week after operation for a left temporal oligodendroglioma (left, Goldmann; right, automatic perimetry). b: same tests four months after surgery.*

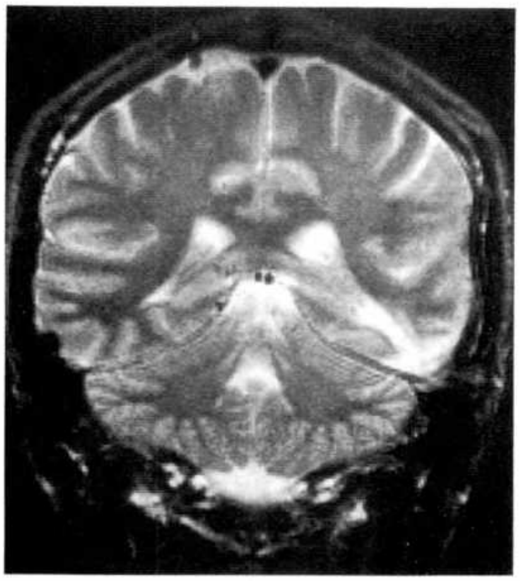

*Figure 8 Case 4. Coronal T2-weighted MRI picture showing the left temporal basal postsurgical lesion (right side of picture).*

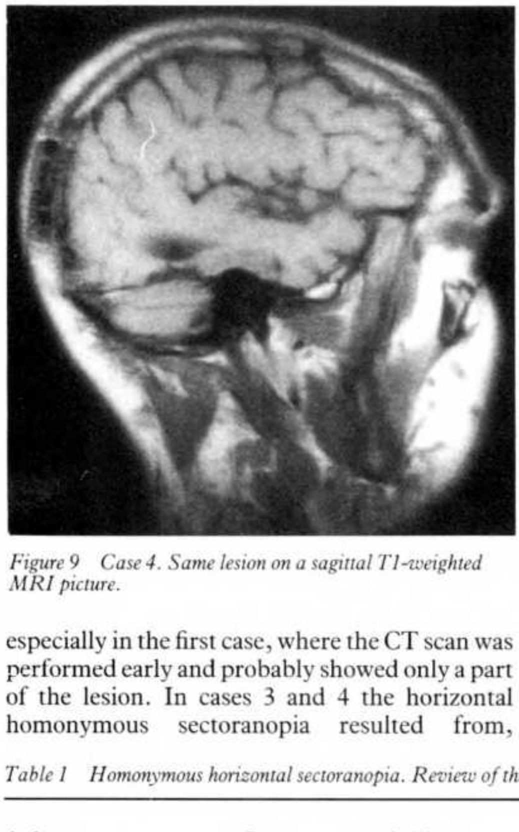

*Figure 9 Case 4. Same lesion on a sagittal T1-weighted MRI picture.*

especially in the first case, where the CT scan was performed early and probably showed only a part of the lesion. In cases 3 and 4 the horizontal homonymous sectoranopia resulted from, respectively, a wound of lateral sinus and resection of a temporal lobe tumour. An alteration of the optic radiations appeared likely on the CT scan, showing a superficial involvement of the temporal lobe in case 3 (Fig 6). In case 4 the lesion was located in the posterior and inferior part of the left temporal lobe. These patients had no lesion in common. Involvement of the lateral geniculate nucleus seemed very unlikely in these cases. However, an alteration of the LGN may not be easily recognised on a first CT scan when the causative mechanism is vascular. A second CT scan a few days after the beginning of the visual trouble may be necessary.[5]

The follow-up of our last two cases showed a partial regression of the surface of the visual field defect. In the first case it was associated with the resolution of the intracranial hypertension and in the second with the resolution of the post-operative trauma. The evolution is not always well documented. A complete return to normal of the visual field is possible.[8] The visual field defect may persist without modification,[1,9] or shrink to a small triangular paracentral scotoma,[7] or increase with the progression of the causal disease,[1,2,10] giving a classical hemianopic pattern.[2] When the LGN is involved, it seems possible to explain homonymous sectoranopia easily by anatomical arguments.[2,3] When the lesion responsible is more diffuse and when the optic radiations are involved, anatomical correlations are less easy to effect. Since Spalding's study[7] to our knowledge there have been no extensive studies permitting a precise correlation between visual field patterns and alteration of the optic radiations.

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*Table 1 Homonymous horizontal sectoranopia. Review of the literature*

| *Authors* | *Cases* | *Aetiology* | *Topography* | *Visual field defect* |
|---|---|---|---|---|
| *Cases without CT scan* | | | | |
| 1931 Holmes[1] | F32 | Angioma | Occipital lobe (patho) | Left |
| 1952 Spalding[7] | 4 cases | Wound | Optic radiations | Left (case 5) |
| 1969 Oosterhuis *et al*[8] | M25 | Vascular | Temporooccipital junction | Left |
| 1970 Smith[9] | M38 | Vascular probably | Optic radiations | Left |
| 1971 Gunderson, Hoyt[2] | M24 | Astrocytoma | LGN (patho) | Left |
| 1978 Frisen[4] | F33* | AV malformation | LGN | Left |
| | M43 | Vascular thrombosis | LGN | Left |
| 1984 Schacklett *et al*[5] | F52 | AV malformation | LGN | Left |
| | F52 | Astrocytoma | LGN | Left |
| 1985 Carter *et al*[10] | M26 | Astrocytoma | Temporal posterior lobe | Left |
| | F35 | AV malformation | Parietotemporal lobe | Left |
| 1988 Nakahashi *et al*[6] | M76 | Ischaemic | LGN | Left |
| 1990 Grossmann *et al*[11] | F77 | Ischaemic | Occipital lobe | Left |
| 1990 Our cases | F66 | Ischaemic | Superficial sylvian art. territory | Right |
| | M59 | Ischaemic | Ant. choroidial art. territory | Right |
| | M28 | Wound | Temporal lobe | Right |
| | M25 | Surgical wound (oligodendroglioma) | Temporal-occipital junction | Right |

*Arteriographic investigation only.
LGN=lateral geniculate nucleus. AV=arteriovenous. Patho=pathological study. Art=artery. Ant=anterior.

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# Synergism between diabetic and radiation retinopathy: case report and review

Martin Viebahn, Michael E Barricks, Mark D Osterloh

**Abstract**

**It is suspected that radiation retinopathy is more likely to develop in an eye with pre-existing diabetic retinopathy than in a normal eye. However, there is only one report of this occurring, at a radiation dose of 4500 rads. We present a woman with minimal diabetic retinopathy who had breast carcinoma which was treated with chemotherapy but metastasised to the choroid. Within nine months of external beam radiation (3000 rads in fractions of 200 rads) a fulminant retinopathy evolved in that eye, while the non-radiated eye showed no change. The histopathology of radiation and diabetic retinopathy and causes for possible synergism are discussed. As this case report shows, radiation oncologists and ophthalmologists need to be aware of the risk that patients with minimal diabetic retinopathy who have undergone chemotherapy may suffer a dramatic visual loss from radiation therapy despite a radiation dose which is considered adequate, safe, and properly fractionated.**

Radiation damage in tissues may result from direct parenchymal damage, usually in a rapidly dividing cell system such as intestinal epithelium, or from delayed effects caused by damage to vascular and interstitial support structures.[1] In the eye, radiation retinopathy is a disease resulting from damage to retinal blood vessels.[2-5] Gass states that, clinically and angiographically, radiation retinopathy is virtually identical to diabetic retinopathy.[6]

Several authors have noted that patients with diabetes or hypertension may be particularly susceptible to radiation induced vascular damage.[1 5 7 8] However, we could find only one case report of this occurring. In this case a moderate radiation dose (4500 rads was given to the fovea by cobalt-60 plaque irradiation) caused radiation retinopathy in a diabetic patient.[5] Chemotherapy is also thought to augment the damaging effects of radiation to the posterior segment of the eye even if it is not concomitant with radiation.[1 5 7]

In this paper we describe a case of a woman in which the combined effects of pre-existing minimal diabetic retinopathy, previous chemotherapy, and radiation therapy led to a fulminant retinopathy despite a dose of external beam radiation which was considered adequate, safe, and properly fractionated.

## Case report

The patient is a 54-year-old woman with known insulin dependent diabetes mellitus for 16 years and minimal background diabetic retinopathy. She is otherwise healthy and has no cardiovascular or carotid artery disease. At the age of 45 she underwent a modified radical mastectomy for breast cancer. Since the tumour had spread to adjacent lymph nodes the patient received a full course of cyclophosphamide, methotrexate, and 5-fluorouracil. She developed a cough seven years later, and a mediastinoscopy confirmed the presence of metastatic adenocarcinoma, which has been treated with tamoxifen since.

Nine years after diagnosis of the primary tumour the patient noted photopsias in the right eye. Examination showed a best corrected visual acuity of 20/30 and 20/25 in the right and left eye respectively. There was slight congestion of episcleral vessels of the right eye nasally. Both eyes showed minimal background diabetic retinopathy with a few microaneurysms and dot haemorrhages (Figs 1 and 2). In the right fundus a creamy white choroidal lesion between 3 and 5

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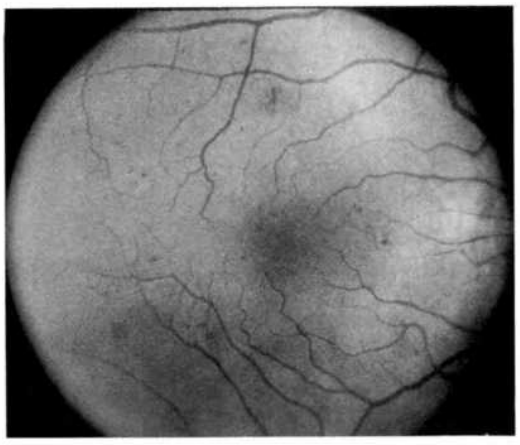

*Figure 1 Red-free photograph of the right eye shows minimal background diabetic retinopathy changes with a few microaneurysms and dot haemorrhages.*

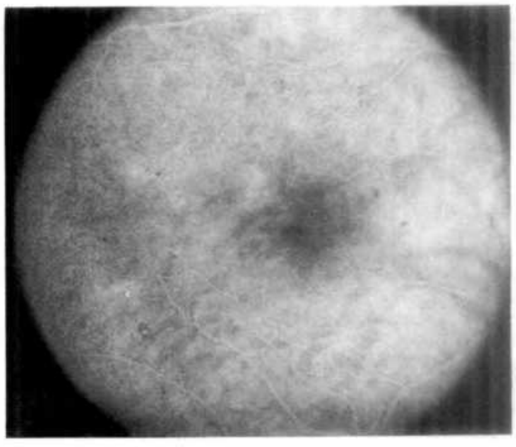

*Figure 2 Fluorescein angiogram of the right eye shows microaneurysms and blockage of background choroidal fluorescence by intraretinal haemorrhages (242 seconds after dye injection).*

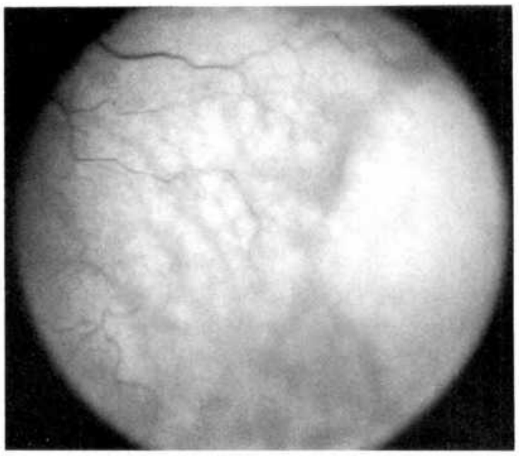

*Figure 3 Red-free photograph of the choroidal mass with secondary shallow retinal detachment in the inferonasal periphery of the right eye representing metastatic breast carcinoma.*

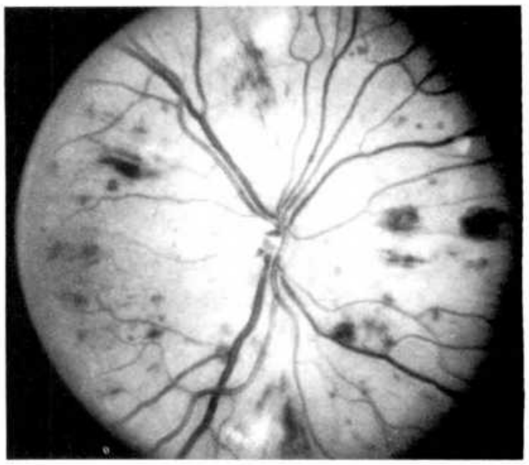

*Figure 4 The red-free photograph of the right eye exhibits progression with intraretinal haemorrhages and appearance of cotton-wool spots seven months after radiation therapy.*

o'clock in the far inferonasal periphery with secondary shallow retinal detachment was noted, consistent with metastatic carcinoma (Fig 3). A fluorescein angiogram showed very early leakage from this mass lesion which continued throughout the course of the study. A diagnosis of choroidal metastasis from primary breast carcinoma was made. With the 4 MeV linear accelerator the lesion was treated with a total of 3000 rads over three weeks, in fractions of 200 rads.

One month after treatment the secondary retinal detachment had disappeared. The visual acuity and the appearance of mild background diabetic retinopathy were unchanged. Six months after radiotherapy the visual acuity remained unchanged but the retinopathy had markedly increased in the right eye. Cotton-wool spots were now present as well as increased haemorrhages and oedema. Seven months after radiation visual acuity in the right eye had decreased to 20/80, and a fluorescein angiogram showed early perifoveal capillary loss as well as haemorrhages and peripheral capillary loss (Figs 4 and 5). Nine months after radiotherapy the vision in the right eye, was hand motions and severe capillary dropout was seen (Figs 6 and 7). The left eye remained unchanged with 20/25 visual acuity and minimal background diabetic retinopathy (Fig 8).

## Discussion

The first report of radiation retinopathy was published in the 1930s in a case of implantation of radon seeds for the treatment of a retinoblastoma.[9,10] Subsequent reports have described the typical clinical and angiographic changes of radiation retinopathy.[2-5,8,11,12] Clinically one may see microaneurysms, intraretinal oedema, exudation, and haemorrhage. Retinal telangiectasis, neovascularisation, cotton-wool spots, and vascular sheathing are also seen. Ischaemic optic neuropathy may occur as well as vitreous haemorrhage and retinal detachment. The posterior pole of the eye appears to be the area most sensitive to radiation damage.[3,5] On fluorescein angiography the most striking finding is severe retinal capillary non-perfusion.[2,4-6] Histologically the walls of small retinal vessels are thickened, and there is loss of endothelial cells.[4,5,11,13] In experiements on monkeys Irvine and Wood[14] demonstrated that the retinal capillaries are damaged first. In their trypsin digest flat bed preparations there was initial

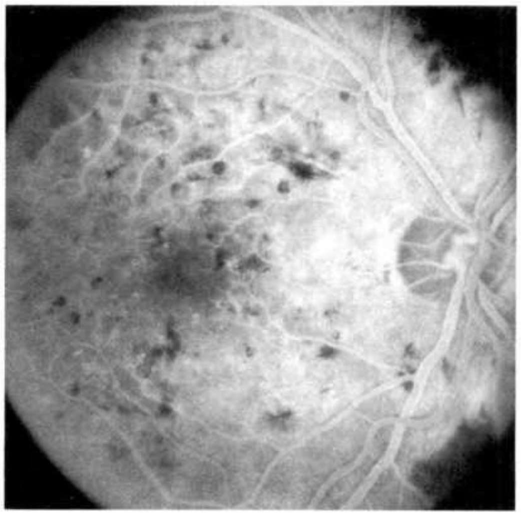

*Figure 5 The fluorescein angiogram of the right eye shows early perifoveal capillary loss seven months after radiation therapy (arteriovenous phase).*

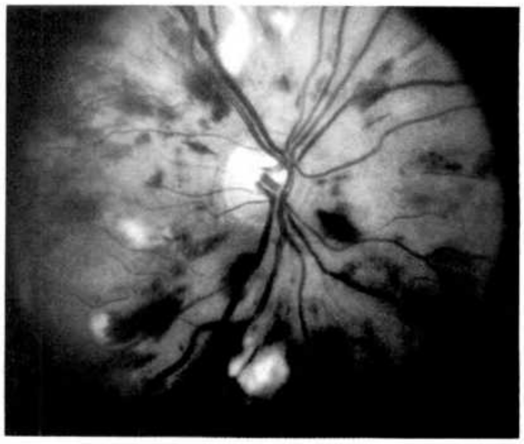

*Figure 6 Further progression of the right eye with significant intraretinal haemorrhages and cotton-wool spots nine months after radiation therapy (red-free photograph).*

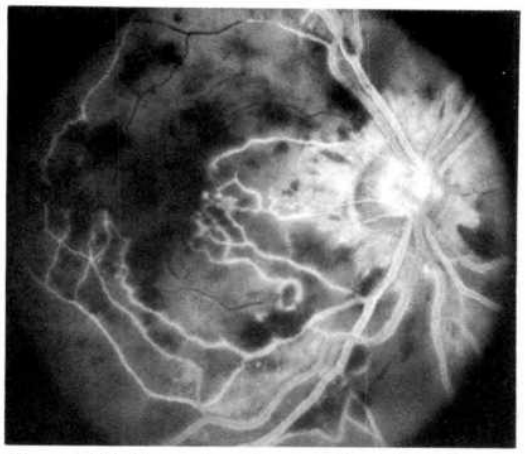

*Figure 7 The fluorescein angiogram of the right eye shows marked capillary non-perfusion nine months after radiation therapy (30.6 seconds after dye injection).*

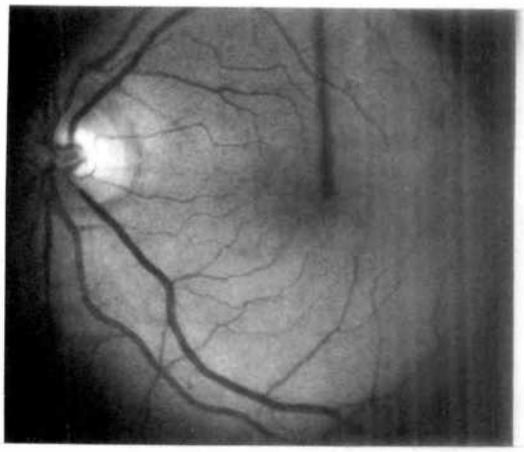

*Figure 8 The left eye remains unchanged, exhibiting minimal background diabetic retinopathy changes with a few microaneurysms and dot haemorrhages (red-free photograph).*

endothelial cell loss and then loss of pericytes, resulting in large areas of capillary non-perfusion. Microaneurysms, closure of bigger vessels, recanalisation, and neovascularisation in the retina and to a smaller degree in the choriocapillaris can be observed later. Electron microscopy confirmed new endothelial cell growth within thickened, recanalised vessels.[14] However, Irvine *et al*[11] had found in an earlier study that endothelial cells initially appeared to be less damaged than pericytes on electron microscopy, contrary to the findings in trypsin digest preparations.

Clinically, radiation retinopathy may develop after ionising radiation reaches the posterior segment of the eye by either local treatment (for example, application of a radioactive plaque) or external beam radiation. The radiation may be given for local intraocular lesions (for example, retinoblastoma, choroidal melanoma, metastatic disease) or for adjacent extraocular lesions (for example, nasopharyngeal or sinus carcinoma, or intracranial tumours).[2-5 7 8 12 15] The severity of the retinopathy is thought to be related to total radiation dosage and to the fractionation of that dosage.[1-3 7 12] The total time of the treatment is also of significance.[1]

There is general agreement that 3000 rads with a standard fractionation of 1000 rads per week in five fractions (200 rads per treatment session), is a safe total dose of external beam radiation, though there are reports in which radiation retinopathy occurred at lower doses.[2 5 8] However, these dosages were reconstructed, and a low energy 220 KV machine was used which has a higher incidence of complications than contemporary radiotherapeutic emitters.[1] The time course of retinopathic changes is variable, with an onset between six months and three years after radiotherapy, but earlier and later changes have been noted.[5] Higher doses of radiation are not known to be associated with a shortened latency period, but the use of adjunct chemotherapy may be.[3 5 11 16]

Conditions thought to enhance the development of radiation vasculopathy include vascular diseases like diabetes, hypertension, collagen vascular disease, or chemotherapy.[1 5 7] However, we found only one previous report in the literature in which a moderate dose of radiation (4500 rads was given to the fovea by cobalt-60 plaque irradiation) caused radiation retinopathy in a diabetic patient.[5] In this study the authors noted that eyes which progressed to total blindness from radiation damage had received chemotherapy more frequently than eyes with less damage. The chemotherapy does not have to be given concurrently with radiation to show this effect.[5]

This case report describes unilateral development of a fulminant retinopathy after orbital radiation and chemotherapy in the setting of minimal background diabetic retinopathy. The patient received 3000 rads in fractions of 200 rads over a three-week period. With our current understanding it is unlikely that in an otherwise normal eye this conservative radiation dose would have led to the described severe and blinding retinopathy. Likewise, the dramatic visual loss was probably not due to mere progression of the pre-existing diabetic retinopathy alone, since the fellow eye was stable throughout the period of observation. This case suggests that pre-existing minimal diabetic retinopathy and prior chemotherapy had a potentiating effect in the pathogenesis of radiation retinopathy. Since both diabetes and radiation primarily cause damage to retinal capillaries, this potentiating effect may not be surprising. In diabetes it has been shown that there is, among other changes such as thickening of basement membrane, an early loss of pericytes.[17-20] In contrast to this, in radiation induced retinopathy endothelial cells may be disproportionately affected. Since endothelial cells and pericytes are the primary cells making up retinal capillaries, destruction of both these elements by the combined effect of diabetes and radiation would leave little cellular support for capillaries and facilitate changes of capillary closure, aneurysms, vessel leakage, and haemorrhage.

As this case report shows, radiation oncologists and ophthalmologists need to be aware of the risk that patients with minimal diabetic retinopathy who have undergone chemotherapy may suffer a dramatic visual loss from radiation therapy despite a radiation dose which is considered adequate, safe, and properly fractionated.

This study was presented at the West Coast Retina Study Club, 26–27 January, 1987, Kona, Hawaii.

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# Diffuse unilateral subacute neuroretinitis

Marcia D Carney, James L Combs

**Abstract**

**The clinical syndrome of diffuse unilateral subacute neuroretinopathy (DUSN) has been characterised in its early and late stages. Different types of migrating worms in the subretinal and intraretinal space have been described as the cause of the clinical syndrome. We observed a patient with a long history of visual loss, vitritis, and a fundus of abnormal appearance where the worm was noted to migrate to different areas over the course of hours.**

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Between 1963 and 1973 thirteen patients were described at Bascom Palmer with a clinical syndrome consisting of decreased vision, inflammatory cells in the vitreous, optic atrophy, vascular attenuation, diffuse and focal retinal pigment epithelial atrophy, and abnormalities of the electroretinographic responses. This was referred to as the 'unilateral wipe-out' syndrome. In 1975 the earlier stages of the clinical syndrome were recognised as including mild optic disc oedema, vitritis, extensive pigment epithelial changes, and yellow-white lesions affecting the deep retina. In 1978 Gass and Scelfo[1] described later stages of the disease characterised by optic atrophy, vascular attenuation, arterial sheathing, and diffuse retinal pigment epithelial changes with focal and course mottling of the pigment epithelium and atrophy. With marked inflammatory disease of the retina and optic nerve, the syndrome was named 'diffuse unilateral subacute neuroretinitis.'

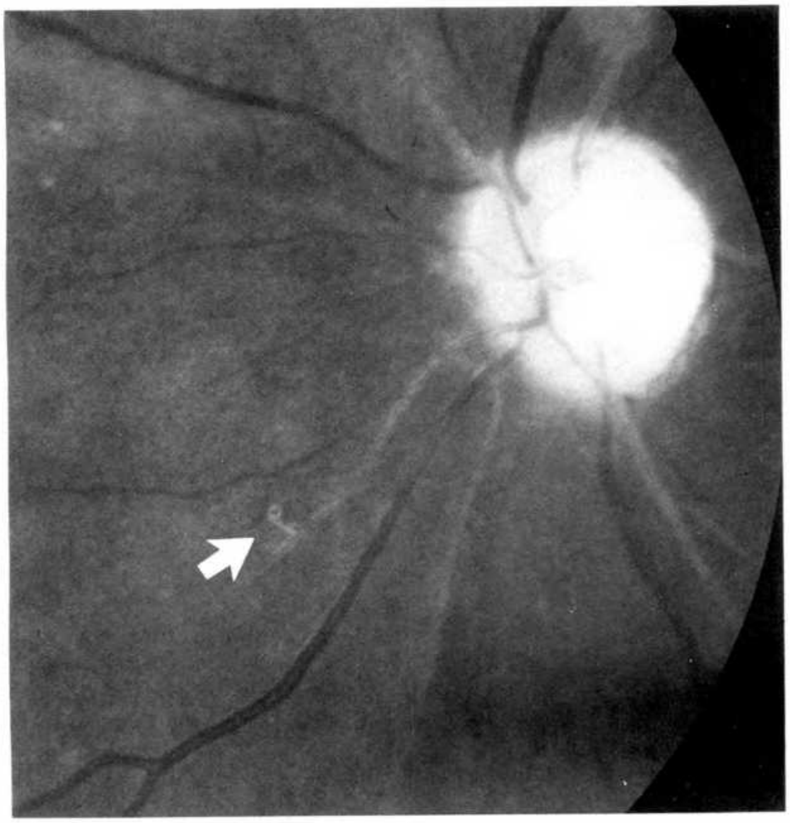

*Figure 1 Left optic disc with nematode in the deep retina (arrow) on 25 November 1987, one disc diameter from the disc, in a dumbbell configuration, along a branch of the inferonasal artery.*

Gass *et al*[2] in 1978 reported 37 more cases. It was suggested from the newer observations that the syndrome may be related to toxic damage to the optic nerve and retina caused by a worm migrating in the subretinal space. Gass *et al* emphasised the early or subacute stage and the appearance of 'successive crops of evanescent lesions', either grey-white or yellow-white, involving the deep layers of the retina. These lesions would fade in several days, leaving colour changes in underlying pigment epithelium. In two of these patients a motile subretinal worm was noted close to active retinal lesions.[2] The changes in the pigment epithelium produced a dull-reflex which was similar to changes noted in a diffuse tapetoretinal degeneration.

The electroretinogram (ERG) was normal in two patients in the early stages of the disease.[2] In the late stages there was more B-wave reduction than A-wave reduction. The ERG was not extinguished in any of the patients.[2] Electrooculograms were abnormal in 16 of 29 performed.[2] It has been suggested that this uniocular syndrome may be caused by several nematodes, with *Baylisascaris procyonis*, the raccoon roundworm, being one possible cause.[3-5]

## Case report

A 22-year-old Liberian woman presented to the Ophthalmology Office of the Medical College of Virginia on 13 August 1987 complaining chiefly of decreased vision in the left eye. Before leaving Liberia in 1979 she was seen by an ophthalmologist. At that time she complained of nyctalopia and decreased vision in the left eye. The condition was essentially stable until two months prior to her visit to the Medical College of Virginia, at which time she noted a further decrease in the visual acuity of the left eye and intermittent micropsia. Her past eye history was otherwise normal. Her seven siblings had no history of nyctalopia or known tapetoretinal degeneration.

On examination she was found to have a visual acuity of 20/20 in the right eye and 20/50 in the affected left eye. There was an afferent pupillary defect in the left eye. The intraocular pressures were normal. There was pallor of the left optic disc, with marked arteriolar attenuation and diffuse patchy retinal pigment epithelial changes without overt bony spicule changes; a decreased macular reflex was present.

The patient was examined by the Neuroophthalmology Service on 9 September 1987. Her visual acuity had decreased to 15/200 in the

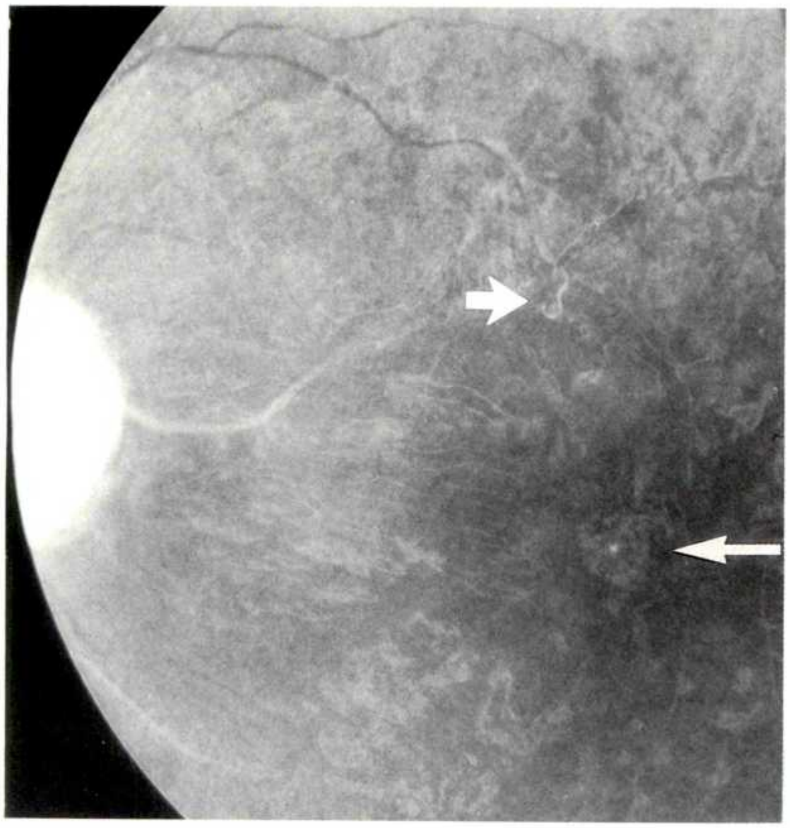

*Figure 2 At 1130 the worm (small arrow) has moved nasally, located in the inner retina superonasal to the fovea (large arrow). Note the tail of the worm overlies the vessel.*

left eye. Colour discrimination was absent in the left eye and normal in the right eye. The fundus was decribed 'as that of a unilateral retinitis pigmentosa'. The right eye yielded visual evoked potential (VEP) and ERG. An absent pattern VEP response was present on the left; the flash VEP response was present. On the left the ERG was absent to photopic stimuli with reduced scotopic A and B waves. On 25 November 1987 while she was being examined, a motile worm was seen inferonasal to the optic disc (Fig 1). It was approximately 800 μm in length and approximately 33 μm in width. The patient returned on 1 December 1987 for follow-up, and the location of the worm was followed for several hours. At 1000 h the worm was seen coiled in the superotemporal macula. At 1130 it had moved nasally in the superior macula (Fig 2). At 1400 the worm was noted to be inferotemporal to the optic disc margin (Fig 3). At 1600 it had moved back into the superior macular area (Fig 4). Light stimulation was used at 1630 to move the worm further into the superior macula area, where photocoagulation was applied.

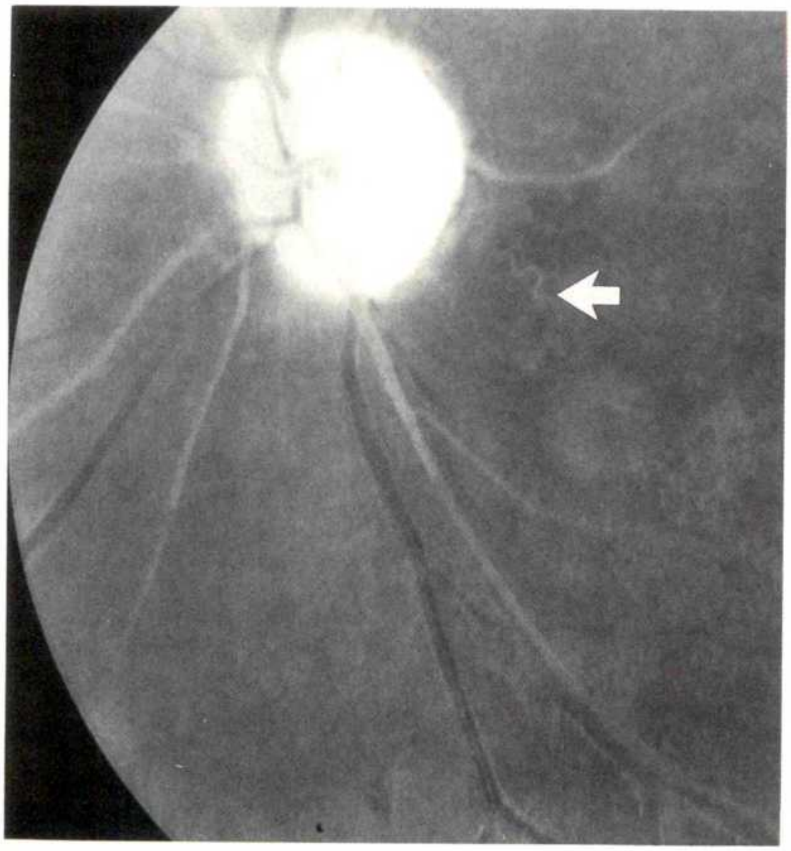

*Figure 3 At 1400 the worm (small arrow) was located inferotemporal to the optic disc margin.*

The patient returned on 2 January 1988. Her visual acuity remained 20/400. No other parasites were noted. The area of laser photocoagulation involving the worm showed evidence of chorioretinal scarring.

## Discussion

Further observations[6-14] have supported those of Gass *et al*[2] that the clinical syndrome of diffuse unilateral subacute neuroretinitis (DUSN) is caused by a nematode. It was initially suggested that this syndrome was caused by *Toxocara canis*.[2] However, evidence has been presented which supports that there are nematodes of two different sizes or nematodes at two different stages of development. Gass and Braunstein[3] on examining 18 patients noted that in 12 the nematode measured 400 to 1000 μm in length; in the other six patients they measured 1500 to 2000 μm. The majority of patients with the smaller nematodes were residing in the south-eastern United States, whereas most of those with the larger nematodes resided in the northern mid-western United States.

Our patient was born in Liberia and moved to the south-eastern United States in 1979. It is noteworthy that her diagnosis of DUSN is suggested prior to her moving from Liberia when, in 1979, at about the age of 14, she was given the diagnosis by an ophthalmologist of a 'circulation problem' of unknown aetiology. There are no other known reports from Africa characterising the size and possible types of nematodes that may cause this syndrome. The worm's size in our patient, approximately 800 μm in length, is within the size category (400–1000 μm) of the nematode found mainly in the south-eastern United States. Like several of the reported patients of Gass *et al*[2] who had reductions in the A or B wave of the electroretinogram, or both, our patient's scotopic electroretinogram had reduced A and B waves and an extinguished photopic ERG.

Kazacos *et al*[5] have made further experimental observations in animals giving support to the possible cause of diffuse unilateral subacute neuroretinitis. Infection by *Baylisascaris procyonis*, the raccoon roundworm, parallels the human infection by *Toxocara canis* in that it is acquired by ingestion of soil containing raccoon ova. The larvae of this parasite are larger than

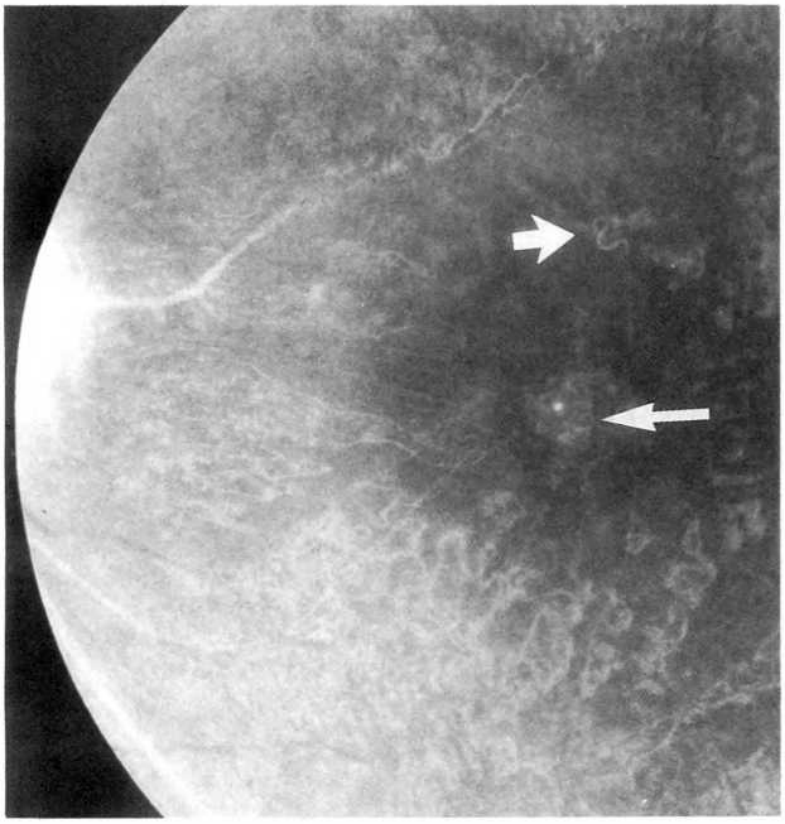

*Figure 4 At 1600 the worm (small arrow) has moved back superotemporal to the fovea (large arrow) beneath the superotemporal artery.*

those of *Toxocara canis*, which average about 400μm.[7,8] Although infection by nematodes of at least two different sizes has been suggested by Gass *et al*,[2] Kazacos *et al*[5] suggest that DUSN is probably caused by a variety of nematode species including *Toxocara* species,[2,3,6] *Baylisascaris procyonis*, and other larvae not yet identified. With the report of exposure to a pet raccoon prior to the onset of visual symptoms in the patient reported by Raymond *et al*[9] and with the more recent reports[10,11] of its zoonotic potential, *B. procyonis* has been suggested as one of the possible causes of the ocular larva migrans syndrome and DUSN.[4,12] Kazacos *et al*[5] have suggested that indeed the two sizes of worms reported by Gass and Braunstein[3] are not inconsistent with the growth range of baylisascaris in infected animals and humans,[10,11,15,16] which may cause many cases of DUSN.

John *et al*[13] have studied the choroidal and retinal response to ascarid-infected eyes in guinea pigs. A closer antigenic relationship exists between baylisascaris and ascaris than between either parasite and toxocara.[13] With intravitreal injection of *Ascarid suum* into guinea pig eyes the resulting response was a diffuse eosinophilic choroiditis, neuroretinal degeneration, and retinal pigment epithelial changes.[13] Intraocular IgE antibody production and mass cell degeneration may lead to the release of a number of eosinophil chemotaxins (eosinophil chemotactic factor of anaphylaxis, histamine). After antigen-antibody complement activation, the focal release of other diffusible eosinophilotactic factors may lead to alterations in the choriocapillaris which contribute to a more generalised and progressive retinal degeneration distant from sites of DUSN. This is probably caused by a number of intraocular nematodes producing a clinical syndrome of decreased visual acuity, anterior uveitis, vitritis, optic disc oedema, and later optic disc atrophy. Diffuse retinal pigment epithelial changes and probable outer and inner retinal damage are suggested by changes in the electro-oculogram and the A and B waves of the electroretinogram.

The worm may cause destructive changes and, as in our patient, lie dormant for years, only to cause further decrease in visual acuity later. Like toxocara, an enzyme-linked immunosorbent assay may soon be available for the diagnosis of *Baylisascaris procyonis* larva migrans or DUSN.[14] Regardless of the type of nematode causing the syndrome, this diagnosis must be considered by the ophthalmologist when patients present with unilateral visual loss of unknown aetiology, particularly when they are young, healthy adults in whom the diagnosis of a 'unilateral retinitis pigmentosa' is considered.

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# Immunohistological and electron microscopical study of nodular fasciitis of the orbit

Taiji Sakamoto, Tatsuro Ishibashi, Yoshitaka Ohnishi, Hajime Inomata

## Abstract

**We report the case of a 7-year-old Japanese girl with nodular fasciitis which was investigated by immunohistological and electron microscopical methods. An excised nodular lesion in her right orbit showed characteristic histological features of the disease. The fibroblastic cells showed myofibroblastic characteristics, such as immunohistochemically positive reactions against muscle specific actin and vimentin and characteristic electron microscopical appearances. The multinuclear giant cells did not react against any histiocytic markers, including HLA-DR, antimacrophage antigen, lysozyme, and S-100 protein, but the myofibroblastic markers and the electron microscopical study did reveal myofibroblastic characters.**

Nodular fasciitis is a proliferation of fibroblastic cells and is one of the commonest tumours of fibrous tissue.[1] Its exact cause is still unknown. However, the disease is benign and does not recur after simple excision.[1] It is most frequent in the upper limbs, but it is rare in the ocular region and its adnexa.[1-10]

Histologically the lesion has been reported to consist of plump fibroblastic cells, some multinuclear giant cells, and a small amount of mature collagen bundles.[1-12] Many authors have reported that these fibroblastic cells are myofibroblasts,[1,3] but the origin of the multinuclear giant cells is still not clearly understood.[3,11,12]

We report a case of orbital nodular fasciitis, having used histological, immunohistological, and electron microscopic techniques to study the origins of the fibroblastic cells and multinuclear giant cells.

## Case report

In October 1989 a healthy 7-year-old Japanese girl noticed a slightly painful mass in the right inner canthus of two months' duration. By March 1990 the lesion had grown rapidly and the mass measured 25×15 mm (Fig 1, arrow). Magnetic resonance imaging showed a solitary nodular mass in the anterior medial part of the right orbit, the hypointense mass on a T1 weighed image, the hyperintense mass on a T2 weighed image (Fig 2, arrow).

On 20 March 1990 the lesion was excised under general anaesthesia. It was a small nodular mass located in the orbit subcutaneously in the right upper eyelid. Six months after the operation the wound had healed well, leaving only a small remnant of the original mass.

### MICROSCOPIC EXAMINATION

The excised mass was cut in half and promptly fixed with neutralised formalin. The paraffin embedded sections were stained with haematoxylin and eosin.

### IMMUNOHISTOCHEMICAL EXAMINATION

Immunostaining was performed on slides prepared from formalin fixed, paraffin embedded tissue by routine avidin-biotin complex (ABC) methods[13] using commercially available polyclonal or monoclonal antibodies with Vectastain ABC kits (Vector Laboratories, Buringame, California, USA). Peroxidase activities were developed in 3, 3′-diaminobenzidine tetrahydrochloride medium (Dojin, Tokyo, Japan). The source and dilution of the antibodies used were as follows: Vimentin: (Dakopatts, Glostrup, Denmark, dilution 1:10); keratin: (MA-902; Enzo Biochem, New York, 1:400); muscle specific actin: (HHF35; Transformation Res, Framingham, Massachusetts, USA, 1:8000); S-100 protein: (Dakopatts, 1:500); HLA-DR: (Dakopatts, 1:40); antimacrophage: (MA935; Enzo Biochem, 1:8000); α-1-

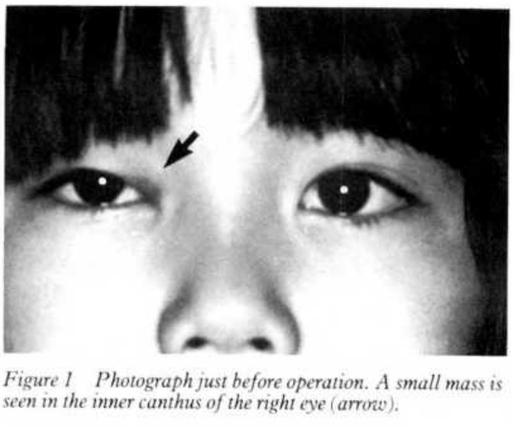

*Figure 1 Photograph just before operation. A small mass is seen in the inner canthus of the right eye (arrow).*

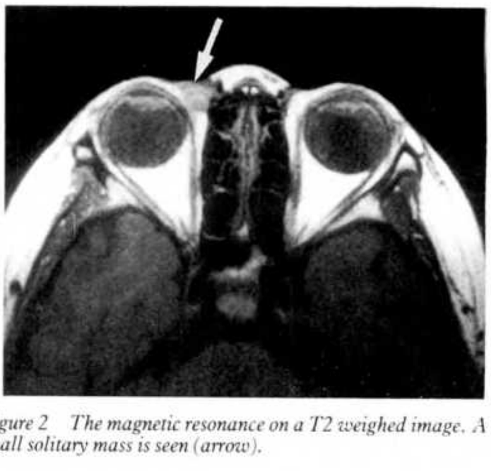

*Figure 2 The magnetic resonance on a T2 weighed image. A small solitary mass is seen (arrow).*

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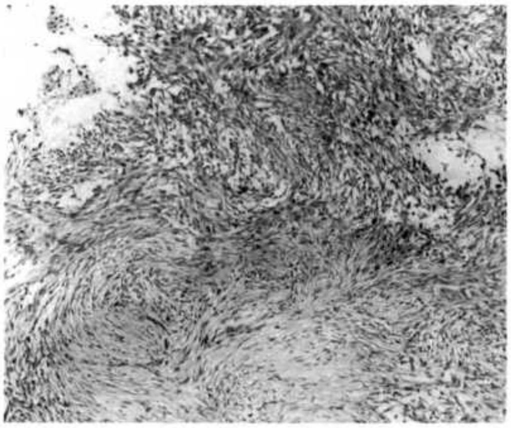

*Figure 3 Low power photograph of the lesion. The spindle shaped cells are proliferating haphazardly in the myxomatous background. (Haematoxylin and eosin, ×40.)*

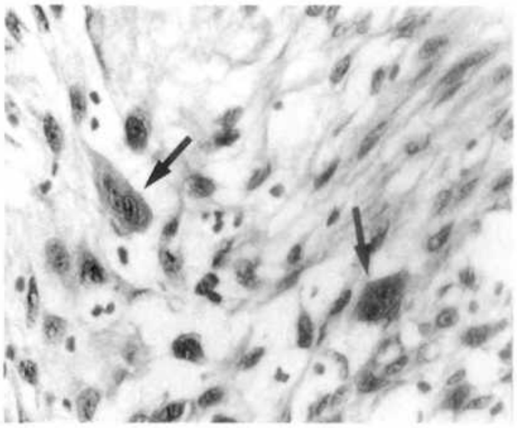

*Figure 4 High power photograph of the lesion. The spindle shaped cell has elongated nuclei but lacks atypical mitotic figures. Extravastated red blood cells are seen, together with multinuclear giant cells (arrows). (Haematoxylin and eosin, ×375.)*

antitrypsin: (Dakopatts, 1:400); and lysozyme: (Dakopatts, 1:400). Anti-S-100 protein antibody, antilysozyme antibody, and alpha-1 antitrypsin antibody were rabbit polyclonal antibodies, while the others were mouse monoclonal antibody.

### ELECTRON MICROSCOPIC EXAMINATION

A small fragment of the resected tissue was fixed with 4% buffered glutaraldehyde solution, postfixed in 1% osmium tetroxide, dehydrated, and embedded in epoxy resin. Thin sections were stained with uranyl acetate-lead citrate and examined with an electron microscope (JEM-100CX, Tokyo, Japan) at an accelerated 80 K voltage.

## Results

### LIGHT MICROSCOPIC FINDINGS

The lesion was composed of plump stellate or spindle-shaped fibroblastic cells, arranged in a parallel haphazard fashion (Fig 3). The nuclei of the fibroblastic cells were round to oval, without atypia. Mitotic figures were only rarely observed. An extravasation of the red blood cells was present, and multinuclear giant cells (Fig 4, arrows) were also noticed in the myxomatous stroma.

### IMMUNOHISTOCHEMICAL FINDINGS

The fibroblastic cells reacted positively with antivimentin and antimuscle specific actin antibodies (Fig 5a), while acting negatively with antimacrophage, anti-HLA DR, antikeratin antibodies, and anti-S-100 protein antibodies. Multinuclear giant cells showed a positive reaction against the antivimentin and antimuscle specific actin antibodies (Fig 5b) but showed a negative reaction to the other markers.

### ELECTRON MICROSCOPIC FINDINGS

The fibroblastic cells had many endoplasmic reticula (Fig 6a). Parallel bundles of actin-like filaments with fusiform densities (Fig 6a, arrows) were present under the plasma membrane. Desmosome-like plaque was noticed between the cells (Fig 6b, arrow).

The multinuclear giant cells had an irregular margin with finger-like processes. A rough endoplasmic reticulum, numerous microfilaments, and dense bodies were also noted in the cytoplasm.

## Discussion

The histopathological study of this case revealed the characteristic findings of nodular fasciitis, such as proliferation of plump spindle-shaped cells located haphazardly within the mucoid

*Figure 5 Immunohistological figures shown by antimuscle specific actin (HHF-35). A: The cytoplasm of the spindle shaped cells was positively stained (arrow). (ABC method, ×350.) B: The multinuclear giant cell also showed positive reaction products in the cytoplasm. (ABC method, ×400.)*

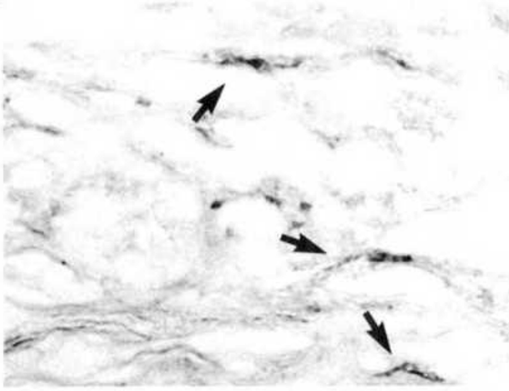

*Figure 5A*

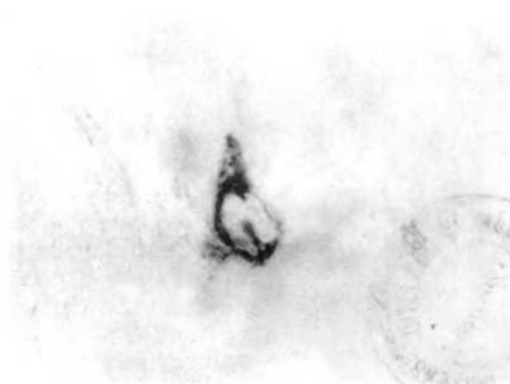

*Figure 5B*

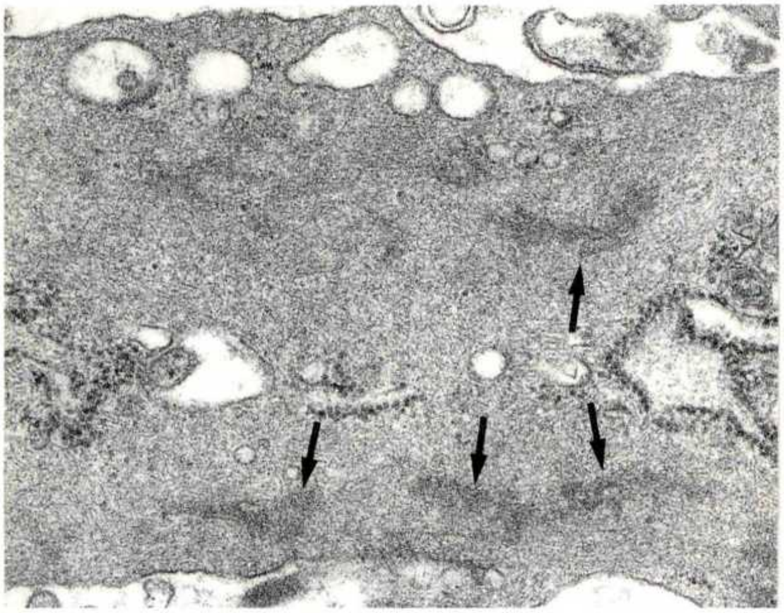

Figure 6A

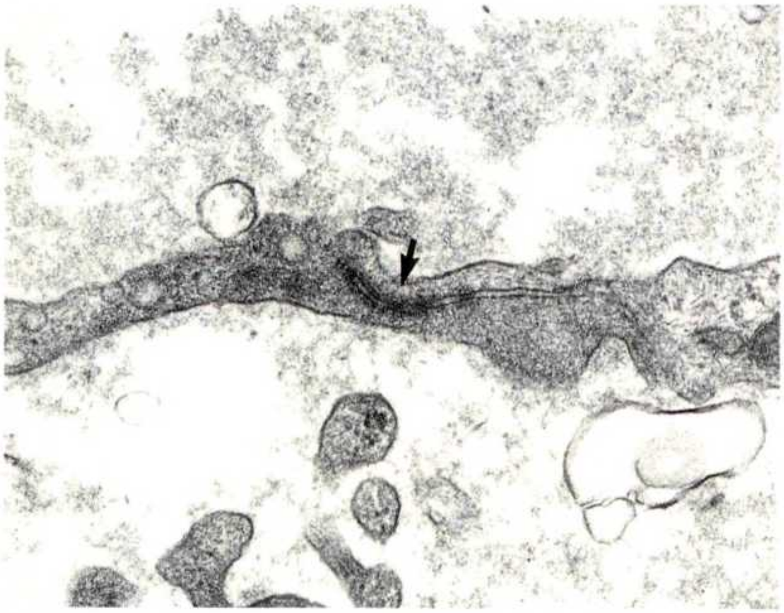

Figure 6B

*Figure 6 Electron-microscopic figures of the spindle cells. A: Bundles of microfilaments with dense bodies (arrows) running parallel to the long axis of the spindle cells. (×38 000.) B: A desmosome-like plaque is present between the spindle shaped cells. (×41 000.)*

matrix and admixed with many multinuclear giant cells.[1,3] These findings have often been mistaken for a sarcomatous lesion or other benign spindle cell lesions.[1] A sarcomatous lesion was ruled out because of the lack of any mitotic figures and cellular atypia.[1] In addition, other benign spindle cell lesions could be excluded by clarifying the characteristics of the cells as follows. The major cells of this case were spindle shaped cells which gave an immunohistologically positive reaction to muscle specific actin and vimentin but a negative reaction to other markers, and we demonstrated dense patches electron microscopically in the cytoplasm and desmosome-like plaques. These appearances were identical with those of the myofibroblasts.[14,15]

On the other hand the presence of multinuclear giant cells was one of the histological features of the disease,[1-12] and these cells were believed to have originated from histiocytes.[3] Recently Okaye and Watanabe reported from electron microscopical findings[11] that multinuclear cells in this lesion originated from myofibroblasts. Diaz-Flores *et al* also suggested that both fibroblastic cells and multinuclear cells originate from vascular pericytes.[12] However, the exact origin of these cells has yet to be elucidated. Immunohistochemically the multinucleate giant cells showed a positive reaction against the antimuscle specific actin and vimentin but a negative reaction against, antimacrophage, α-1-antitrypsin, lysozyme and HLA-DR antibodies, which usually reacted with macrophages.[16-18] The lack of any positive immunohistochemical staining might sometimes be due to poor fixation and embedding procedures, though a positive reaction of the macrophages in the same section further suggested a negative reaction of those giant cells. Electron microscopically the giant cells showed numerous peripheral microfilaments with dense bodies and endoplasmic reticulum, which are a feature of smooth muscle cells.[1,11,14,15]

It might be true that some giant cells showed different immunohistological reactivities (antimuscle specific actin negative) so these possibilities still do not exclude the fact that multinuclear giant cells may have various other different origins. However, in considering both the immunohistological and electron microscopic findings together, we could say at least that some of the multinuclear giant cells originated from the myofibroblasts.

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# LETTERS TO THE EDITOR

## Seasonal variation in congenital toxoplasmosis

SIR,—Ocular toxoplasmosis is the most important cause of posterior uveitis and is considered to represent a late manifestation of congenital infection.[1,2]

At present no definite cure exists for toxoplasmosis so prevention is of utmost importance. In 1984 the WHO urged the initiation of worldwide prevention projects to decrease the frequency of this congenital disease.

The moment of maternal infection during pregnancy was reported as an important factor in the severity and frequency of the fetal infection.[3] Severe congenital toxoplasmosis with either neonatal death or neurologic manifestations and ocular involvement is only encountered if the maternal infection occurs during the first two trimesters of pregnancy. Later acquisition results mostly in subclinical fetal infections and accounts for about 65% of all maternal seroconversions. The cases of ocular toxoplasmosis manifested during adolescence and later are probably due to congenital infections associated with infection of the mother late in the pregnancy.

The aim of this study was to investigate whether the risk of maternal seroconversion depended on seasonal variation. We therefore analysed the birth dates of 532 patients with ocular toxoplasmosis, without evidence of any extraocular symptoms of toxoplasmosis and compared these data with the overall birth rate variation in the Netherlands over the same time period (Fig 1). The diagnosis of ocular toxoplasmosis was made on clinical grounds – in patients with unilateral focal necrotising retinitis sometimes associated with typical old pigmented scars. In doubtful cases an active formation of antitoxoplasmal antibodies in the eye was assessed by the Goldmann-Witmer coefficient.[4] *Toxoplasma* serology was not routinely performed since *Toxoplasma* antibodies are present in the majority of the Dutch population and so positive titres in adults have no diagnostic value. The patients included were those who attended uveitis clinics with active ocular toxoplasmosis between 1987 and 1988. The birth dates of the patients and controls (population study of more than 20 000 persons per year) were between 1954 and 1969.

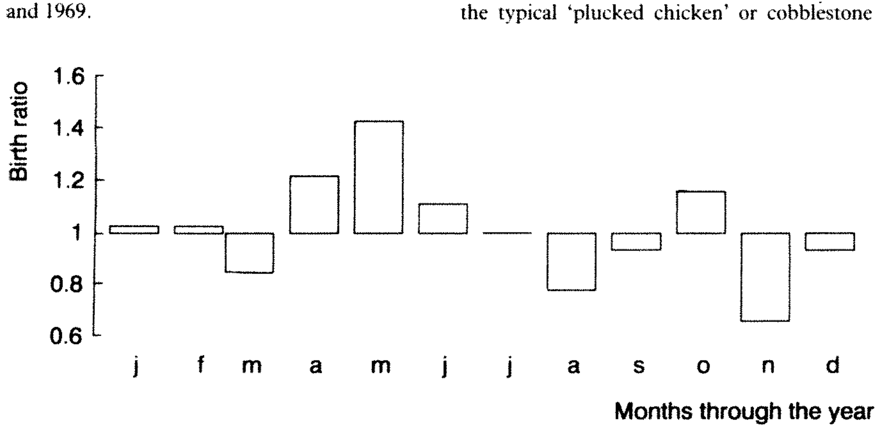

*Figure 1 Seasonal variation in congenital toxoplasmosis.*

$$\textit{Birth ratio} = \frac{\textit{number of children born with ocular toxoplasmosis}}{\textit{expected number}}$$

Two significant differences between the overall birth rates and those of patients were observed: a higher birth rate of children with ocular toxoplasmosis in May and a lower birth rate in November compared with the expected number of births (Fig 1; $\chi^2$ test, $p<0\cdot05$).

How are we to interpret these findings? All our patients had only ocular involvement of toxoplasmosis and so we can assume that the maternal infection probably took place during the third trimester of the pregnancy.[3] A higher frequency of seroconversion in March, April, or May may thus be responsible for a peak of births observed in May.

These findings suggest that there may be a higher risk of contracting toxoplasmosis in the early spring and eventual preventive measures should take this phenomenon into account.

The authors thank the members of the Dutch Uveitis Group for their cooperation.

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## Angioid streaks in β thalassaemia minor

SIR,—A report by Kinsella and Mooney[1] described a 42-year-old woman of Italian origin with coexisting angioid streaks and β thalassaemia minor. Her general physical and cutaneous examination was normal, and a skin biopsy in 1986 showed no histological evidence of pseudoxanthoma elasticum (PXE). She was referred to the dermatology department in November 1989. She had no symptoms referable to her skin but on close questioning agreed that her axillary skin had changed.

On examination lax skin was noted involving the patient's anterior neck and axillae. She had the typical 'plucked chicken' or cobblestone pattern of PXE of the axillae, with more subtle change of her posterolateral neck, accentuated by stretching the skin. A 4 mm punch biopsy obtained from clinically involved axillary skin and stained with haematoxylin and eosin and Miller's elastic stain and von Kossa reagent showed characteristic histological changes of PXE: clumping, disruption, and calcification of the elastic fibres within the dermis. Punch biopsy of the adjacent normal appearing skin showed no histological abnormality.

An association between angioid streaks and PXE has been noted in at least 62% of cases of angioid streaks.[2] The cutaneous lesions of PXE usually first appear before age 10, but may be delayed until the fourth[3] or fifth decade.[4] Early changes are frequently clinically subtle. On occasion a histological change consisting of tiny foci of abnormal elastic tissue may be detected in skin which is not clinically altered.[5] Random biopsy of skin is unlikely to be helpful in establishing a diagnosis of PXE. The sites of predilection include the side of the neck, said to be the earliest, most frequent, and most heavily involved site in PXE, and next the axillary areas.[3] Improved diagnostic yield may be attained by taking biopsy samples from scars.[6]

In addition to PXE, angioid streaks have been described in various haemoglobinopathies, and there are single case reports of their occurrence in some thalassaemias.[1] The prevalence of angioid streaks in Paget's disease has recently come under scrutiny. A surprisingly low prevalence of 1·4% was noted, leading to the conclusion that Paget's disease is only infrequently associated with angioid streaks.[7]

Patients with angioid streaks of undetermined aetiology warrant careful clinical cutaneous evaluation with selective histological sampling to detect subtle changes of possible aetiological significance. If clinical examination and skin histology prove normal, these patients should be followed up until the fourth or fifth decade for possible subsequent development of PXE.

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## Pattern visual evoked potential in ocular hypertension

SIR,—Drs Bray, Mitchell, and Howe are to be congratulated on their article on the prognostic significance of the pattern visual evoked potential in ocular hypertension.[1] They say that they are the first to demonstrate such a prognostic significance for abnormalities found on electrophysiologic testing. In so doing they help ophthalmologists faced with ever mounting numbers of ocular hypertensive patients to decide which patients are at risk of developing glaucoma and therefore worthy of prophylactic treatment. However, before adopting their test strategy as a routine it would be helpful if they could amplify the precautions they took in this prospective study to truly identify those ocular hypertensive patients with an abnormal VEP who progress and develop a visual field defect.

In their article they describe the results of twice testing 49 ocular hypertensive patients with VEP and perimetry, first between 1984 and early 1989, and secondly in late 1989. They note that 7/24 (29%) reverted to normal. It would be helpful to know what was the test-retest variability in their laboratory.

Secondly, these patients had only two visual field tests analysed. Assuming that they had had previous tests and were 'experienced' patients, there are still many pitfalls found on drawing conclusions from analysing two visual fields, especially in glaucoma patients,[2-4] for the visual field can progress from 'normal' to 'abnormal' (and then back again) in consecutive fields. The authors should let us know the precautions taken to rule out such false positive results occurring in their patients.

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### Reply

Sir,—We would like to thank Mr Hitchings for making a number of important observations. With regard to the false positive rate of the VEP, as we explain in discussion, intertest comparisons enable us to detect deterioration of VEP parameters, and thus abnormality, even when they still fall within the normal range. So, while it is true that the VEP of seven of our ocular hypertensive (OH) patients were reported as 'normal' on repeat testing, we are able to qualify these observations. In four of the seven cases such comparisons revealed an increase in latency in the fellow eye, 'normalising' a previously reported interocular difference, but nevertheless suggesting 'abnormality.' Of the other three, one was found to have consistently normal intraocular pressures during subsequent follow-up and in retrospect we feel should have been eliminated from the trial, and one who became 'normal' when he changed age control range (59 to 60 yr). This leaves one false positive for whom we have no explanation. Notwithstanding this, the true false positive rate of 3/24 (12·5%) is similar to that observed in the control group (2/26 or 7·7%) and within the degree of statistical precision one would expect from a trial of this size. Test-retest variability was investigated in four control subjects who were subjected to daily VEPs for three days. Mean intertest latency for this group was found to be 1·8 ms. Intertest interocular variability is insignificant, as it is less than the measurement accuracy of VEPs.

In relation to the second question, we acknowledge the current view that more than two static fields are required to make a firm diagnosis and concede the weakness of our study in this respect. However, in partial defence of our position, glaucoma was not diagnosed in those initially defined as OH on the basis of kinetic perimetry unless corresponding field defects were found on both Goldmann and Octopus perimetry. This procedure was adopted as a precaution against false positives and to ensure that their diagnoses had not changed from OH to glaucoma solely as a result of the use of computerised static perimetry. By this method field defects were confirmed in six of the seven patients. The other patient, who was subjected to Octopus perimetry alone, had 'pristine' fields on initial testing and subsequently developed a field defect involving points with up to 16 dB of loss of sensitivity within 12° of fixation. Both Heijl and Piltz have observed that points with normal or near normal sensitivity show the least intertest variability, and this is lowest in the most central portion of the field. Based on these observations, we are confident of our diagnosis in this case though we accept that intertest variability introduces a measure of uncertainty.

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# OBITUARY

## E G Atkinson, *MBChB, MSc, MRCP*

Edmund Atkinson had just resumed his clinical training in ophthalmology, after three years in research, when he died in a paragliding accident in France in June 1990. He had been an invaluable and enthusiastic member of the retinal vasculitis research group at St Thomas's Hospital, and presented his work both at the OSUK and ARVO. He qualified in medicine at Bristol University in 1982, and obtained his MRCP after working in local hospitals. He then moved to London to start his career in ophthalmology at St Bartholomew's Hospital. As he wished to develop his research interests as soon as possible he moved to St Thomas's Hospital, where in 1986 he became an MRC Training Fellow. He developed two new animal models of uveitis, and extended earlier work on its pharmacological modulation. Later he worked with the pharmacology department to develop FITC-dextran angiography as a method for investigating permeability changes in human uveitis. At the time of his death, he was continuing his studies on cloning vitreous T-cells from uveitis patients. He was always a potent source of ideas, support, and enthusiasm and always wished to stretch his many talents to the full. It was tragic that his latest enthusiasm should also be the cause of his early death.

CE

# NOTES

### The 4th Annual Meeting of the Retinological Society (Retinologische Gesellschaft)

The 4th Annual Meeting of the Retinological Society (Retinologische Gesellschaft) will be held on 1 to 2 November 1991, at the Kupferbau-Buildung of the University of Tübingen, Gmelinstrasse 8, W-7400 Tübingen, Germany. Details from: Professor I Kreissig MD, Ophthalmology III, Schleichstrasse 12, W-7400 Tübingen, Germany. (Tel: 07071/293741, Fax: 07071–293730.)

### Optical engineering

A meeting on Ophthalmic Technologies II (Part 2 of Biomedical Optics) will be held by the International Society for Optical Engineering on 19–24 January 1992. It will be at the Los Angeles Airport Marriott Hotel, Los Angeles, California, USA. Details from the society at PO Box 10, Bellingham, Washington 98227–0010, USA

### Golden Jubilee Conference of All India Ophthalmological Society

The Golden Jubilee Conference of the All India Ophthalmological Society will be held in New Delhi from 2 to 6 February 1992, at the Ashok/Samrat Hotel. Further details: Dr R B Jain, organising secretary, Mohan Eye Institute, 11-B Ganga Ram Hospital Marg, New Delhi-110 060, India. (Tel: 587655, 5728969. Fax: 91–011–5728969).

### First International Skull Base Congress

This congress, sponsored by the Skull Base Societies around the world, will be held on 14–20 June 1992 in Hannover, Germany, headed by Professor Dr med Professor H C Madjid Samii, Medical University of Hannover. A major event of this congress will be a special session on orbital diseases and surgery covering all aspects of an interdisciplinary approach. Further information from: Professor Dr M Samii, Director of the Clinic of Neurosurgery, Krankenhaus Nordstadt, Haltenhoffstrasse 41, D-3000 Hannover 1, Germany. (Tel: 0049-(0) 511–76 38 178, 76 38 606.)

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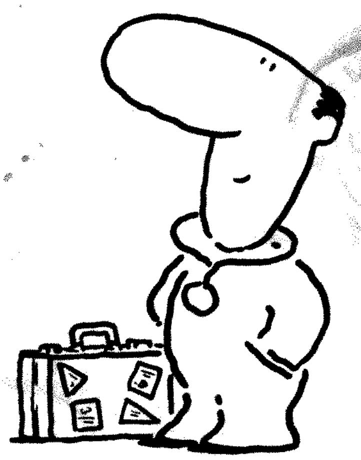

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## *Editorial*

# Herpes simplex latency and the eye

The herpes simplex virus (HSV) exerts its ocular damage by recurrent corneal infection, having lain dormant in the host tissues for some time. Latency of the virus is an essential part of its natural history, yet the mechanism of latency and recurrence has, for both the clinician and the research worker, remained an enigma.

The definition of HSV latency has been described as the capacity of the virus to exist in a host cell for an extended period of time in a virion-free state and, upon stimulation, to reactivate and replicate to produce infectious progeny virions.[1]

As a result of recent advances in molecular biology and genetics, the phenomenon of latency and reactivation is now being explained in terms of specific chemical components found or localised in the chromosomes. After primary infection, usually of ectodermally derived tissues, the viral genetic material travels by fast axonal transport as a nuclear capside to the site of latency, either the trigeminal ganlgion or other extraneuronal sites, where it exists in an extrachromosomal state as a circular episome.[2] HSV reactivation can be thought of in terms of the classic Crick model of the HSV DNA molecule acting as a template to use the host cell DNA to copy or express, by DNA replication, the HSV genetic information which is transmitted (by transcription) into RNA nucleic acid, which in turn directs the synthesis in the host cell of the specific HSV protein to manufacture the entire virus. Genetic studies have shown that during the acute productive infection many genes are expressed, including the immediate early, early and late viral genes. During latent infection, when the virus is in a non-replicating but transcriptionally active state, only part of the genome is present, specifying latency associated transcripts (LATs), of which four have been identified from the viral DNA strand opposite that which encodes the infected cell protein ICPO, an immediately early regulatory protein. The LATs overlap at least 30% of the terminus of this protein but the transcription pattern of the LAT encoding region is complex and, as yet, not fully defined. The exact localisation of the genes concerned with the establishment, maintenance and reactivation of latency remain unknown, nor has any protein been found associated with these functions.

It has been suggested that reactivation involves expression of a subset of genes, which pass to the surface tissue, such as cornea or skin, initiating a replication cascade and leading ultimately to corneal involvement or skin vesicles.

The mechanism which controls the switch between acute and latent phases of infection is poorly understood. Expression of LATs is not essential for the maintenance of latency[3] but is concerned in viral reactivation. This has been demonstrated by the finding that viral strains lacking LATs can still establish latency in the experimental animal, but have reduced recurrence rates compared with those strains with a LAT present.[4,5] (See ref 6 for overall review.) It has been suggested that promoters of LATs of herpes simplex come from a local tissue response. It is likely that a number of reactivation inducing stimuli in humans occur, including ultraviolet irradiation, trauma and the experimental process of iontophoresis of adrenaline into the cornea. Prostaglandins have been thought to be implicated in the reactivation of viral latency.[7] Indomethazine, a potent inhibitor of prostaglandin synthesis, has been shown to reversibly inhibit the reactivation of HSV from experimental latently infected ganglia.[8] In mammalian cells such stimuli lead to release of an agent which interacts with a cell surface receptor activating adenylate cyclase which synthesises cyclic adenosine monophosphate, a cyclic nucleotide that regulates a large number of metabolic processes and is derived from ATP.

The DNA sequence of HSV Type 1 contains an adenine phosphate monophosphate response element in the enhancer region of the LAT promoter. Cyclic adenosine monophosphate binds to the regulatory subunit of cyclic adenosine monophosphate dependent protein kinases, releasing active catalytic subunits that can phosphorylate specific transcription factors. Such a factor or phosphoroprotein has been identified in HSV[9] and is believed to be involved in regulating many cyclic adenosine monophosphate inducible genes.[10] This suggests that tissue responses have a role in triggering viral reactivation.[11]

Whilst there is no doubt that trigeminal ganglia are the main source of latent HSV in the eye, with up to 20 copies of viral DNA per latently infected neuron being present,[6] the question remains whether the cornea is also a site of herpes simplex latency.

In animal work, HSV has been isolated from rabbit cornea after organ culture but with varying frequency, sometimes depending on the strain of virus used. In the rabbit model, after corneal inoculation with the virus, adrenaline corneal iontophoresis resulted in the virus reappearing only in those animals that had been inoculated with virus strains in which LATs were expressed, and not in those where it was deficient,[12] Electron microscopic studies of human cornea removed by keratoplasty after previous HSV infection have shown incomplete extracellular viral particles in deep stromal levels[13]; (for review see ref 14), which could signify low grade infection still being present. Organ culture of keratoplasty specimens has resulted in the isolation of viral particles from the cornea, but whilst none of previously infected human corneas showed any clinical signs of active herpetic infection immediately prior to keratoplasty, it is possible that the HSV isolated after these corneas were cultured in tissue culture (organ culture) was either a contaminant or from low grade corneal infection. Although electron microscopic studies only found HSV particles in such corneas after but not before organ culture,[15 16] it is possible that low grade infection persisted with relatively few viral particles present and were missed by the relatively limited numbers of slides examined with the electron microscope.

In situ hybridisation studies using gene probes for the whole HSV genome have found HSV DNA material in 50% of corneas examined 60 days after experimental corneal inoculation.[17] This contrasts with HSV detection rates of between 17 and 24% after experimental or human corneal organ culture,[18 19] but this does not mean that the gene is either functional, or that it is all present.

In situ hybridisation techniques will not pick up small amounts of viral nucleic acids present, so the polymerase chain reaction has been used to amplify and detect any viral DNA and RNA present (for summary of techniques see ref 20).

Latency associated transcripts (LATs RNA) have been found in corneas removed at the time of keratoplasty from patients seropositive to HSV, either with recurrent but clinically quiescent herpes simplex keratitis, or non HSV corneal disease.[21] In this issue Cook *et al*, after experimental corneal HSV infection, during the latent period found HSV DNA from the ICPO/LAT and thymidine kinase (TK) genes in all of the trigeminal ganglia and three of five corneas investigated, signifying that infection had taken place. HSV LAT RNA was found in all of the trigeminal ganglia and 9% of corneas, signifying latency had been established in these areas. The absence of TK RNA in the corneas rules out active low grade corneal infection, but this potential certainly existed as TK DNA was found in both trigeminal ganglia and corneas.

In order to definitely establish that active infection is not taking place, and that the corneal latency has been established after HSV infection, such a study should incorporate both the operational definition of latency and molecular studies involving LATs. This implies that the same corneas be assessed for the absence of infectious HSV protein, the presence of only LATs or other latency associated transcripts, virus only being produced after organ culture, and no virus seen on electron microscopy prior to corneal organ culture. If such LATs are definitely found in the cornea, and the protein that they express can be identified, it should be possible, either by drugs or monoclonal antibodies directed against those herpes proteins, to block either the establishment of latency or reactivation of the HSV. This would lead to the long term goal of prevention of recurrence of HSV from the human cornea.

The cause of herpes simplex induced stromal disease is controversial. Incomplete herpes simplex viral particles have been found in deep stromal levels in quiescent stromal keratitis,[13] complete particles within stromal keratocytes after graft rejection[22] and the cornea has now been shown in this issue to be a potential source of viral latency. This would suggest that local viral replication plays a major part in the pathogenesis of herpes simplex stromal disease, but it is uncertain whether either just viral replication or a local immune response or both are responsible for all the disease process. It does mean though that antiviral chemotherapy is essential in the treatment of this condition and it raises the question whether topical steroids are also required.

For the future, genetic manipulation of the whole HSV genome could result in the manufacture of a non-virulent variant, not expressing latency, that could be used as a vector to transport genes responsible for enzymes deleted or deficient in the target organ as a result of acquired or congenital disease. For instance, the herpes virus could be used to transport genes to those corneas with congenital dystrophies such as classic lattice where amyloid material accumulates, or in macular dystrophy where glycosoaminoglycans accumulates as a result of a defect in the conversion of a glycoprotein precursor.

JAMES McGILL

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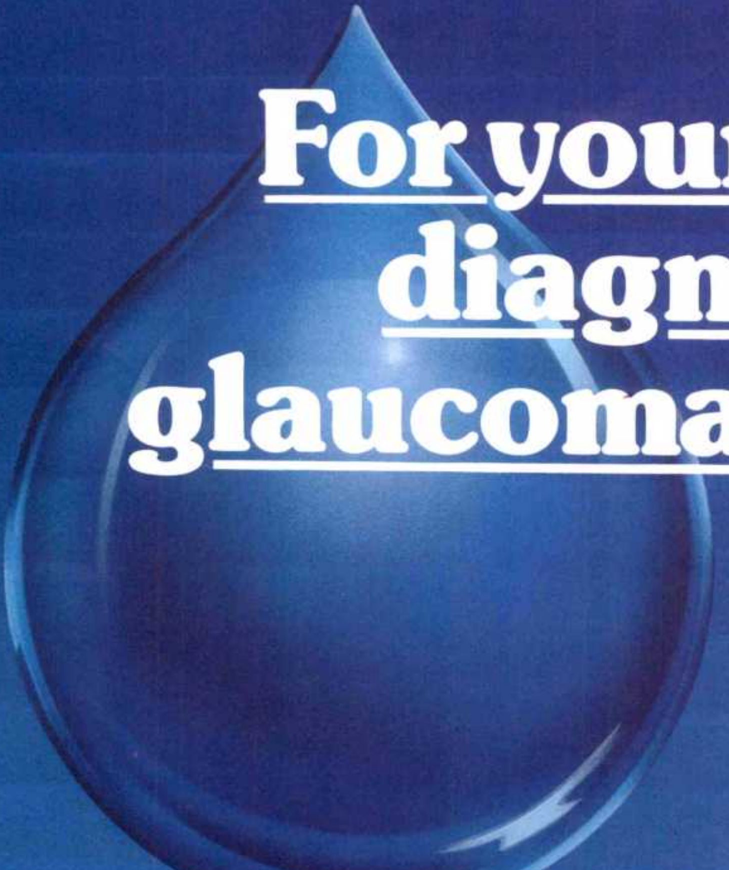

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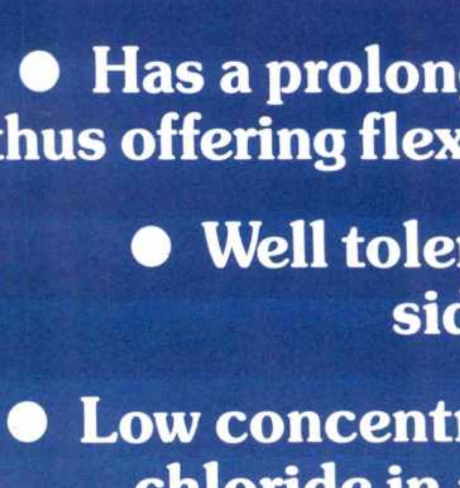

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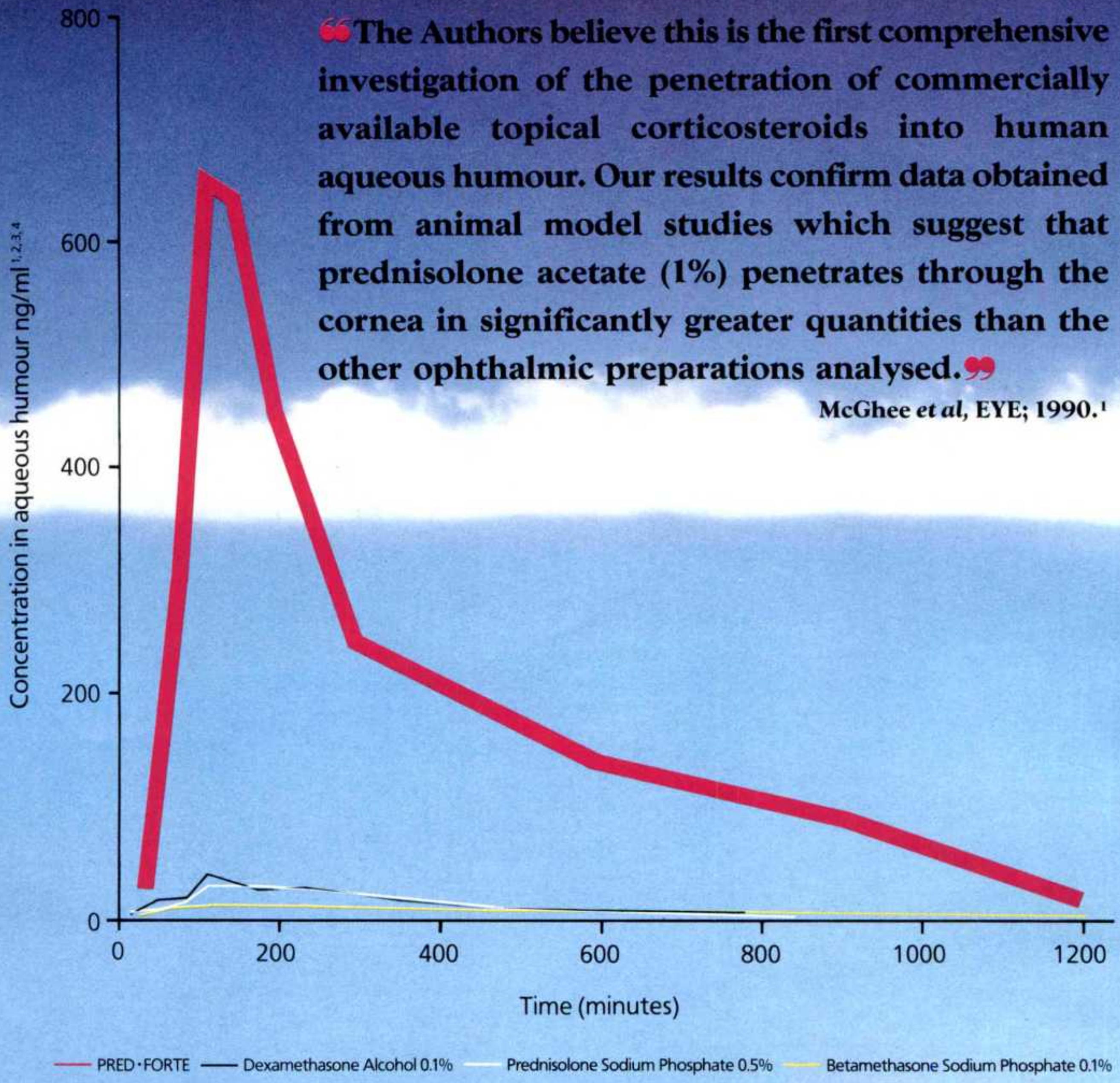

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# *Editorial*

## Pressure and posture

The paper by Yamabayashi and others in this month's issue explores once again the relationship between intraocular pressure (IOP), blood pressure (BP), and posture.

According to Jain and Marmion[1] the postural IOP rise in normal individuals seems to be slightly less than 10% of the sitting IOP. Jain and Marmion also give a useful league table of rises recorded by other authors between 1963 and 1976. The average rise appears to be about 3·22 (higher than that recorded by Jain and Marmion) with a range between 1·40 and 5·00.

In 1978 Williams and Peart,[2] studying cases of branch and central retinal venous obstruction (their term), discovered that whereas the cases had rises of this order (actually 3·10 mm Hg for tributary and 1·8 for central veins) the normal controls only had rises of 0·60 mm Hg, considerably less than those collected by other authors. Both the tributary and central vein cases had moderate vascular hypertension compared with the normal controls. It is of interest that in the cases where the rises were of approximately similar magnitude in each eye regardless of which had the venous obstruction, in fact in some the rise was greater on the unaffected side. This suggests that a systemic factor was responsible for the enhanced rise rather than a local event in the eye, such as the retinal venous obstruction.

It would be natural to assume that the difference was attributable directly to the difference in BP between the two groups but the authors seem to have rejected this, preferring the possible explanation for the difference between normals and controls as being due to a local ocular abnormality in both the affected and the fellow eye. Co-existing glaucoma was the obvious possibility because at the time it was widely believed that pre-existing glaucoma and retinal venous occlusions were associated. However, the association of glaucoma with venous occlusion is now known not to be as straightforward as was once believed and indeed Cole and colleagues[3] showed that the principal medical irregularities which might reasonably be expected to be associated with retinal venous accidents (hypertension and hyperlipidaemia) were just as common in venous occlusion cases with glaucoma as in those without.

One has to ask the question, therefore, why did Williams and Peart reject the BP differences as explaining the postural IOP differences? One reason seems to have been inability to correlate postural IOP changes with postural BP changes (as distinct from the very significant differences in sitting BP between the groups). Another reason is the presence of similar anomalies in a further study of diabetics[4] where like differences were found and were thought not to be correlated with hypertension (although it has to be said that eight of the 14 diabetic patients were hypertensive).

The current paper by Yamabayashi and colleagues is not entirely comparable with the previous papers of Williams and colleagues since the earlier papers deal with differences between normals and patients with vascular hypertension whereas the current paper is concerned with possible differences between normals and ocular hypertensives and low-tension glaucomas. The Yamabayashi paper is interesting in that very little difference was found between the various groups, the normals having rises of the same magnitude (4·4 mm Hg) as the ocular hypertensives or low tension glaucomas. There was admittedly a further rise in the ocular hypertensives after 30 minutes but it was of relatively low magnitude (1·60 mm Hg).

The chief difference between the present paper and those of Williams and colleagues is in the results for the normals. It is not easy to understand why one group of workers should have found such a small rise in normals (0·60 mm Hg repeated in two separate studies) compared with the substantial rise in normals reported in the present paper, but it is perhaps rather characteristic of this particular type of study. There have been a considerable number of fairly similar studies linking posture and IOP, most of which are provided as references in the current paper, but having looked at most of them one is left with rather a vague impression as to how to interpret the results. Apart from the discrepancy between the controls just quoted there is another discrepancy concerning low tension glaucoma in which Yamabayashi *et al* point out that their results, in which such cases have similar rises to ocular hypertensives, are at variance with previous work where low tension glaucomas seemed most susceptible to postural pressure elevation.

One is left with the impression that although the postural changes are of interest and could lead eventually to a better understanding of the mechanisms of glaucoma, there is as yet no real consensus as to exactly what happens to the ocular dynamics on lying down. It seems most likely to me that the venous pressure is something which should perhaps be studied more closely. What happens to it in vascular hypertension for example? Does the venous pressure behave in the same way in vascular hypertensives and controls on lying down, and how can the venous pressure be monitored? One is uncomfortably conscious, as an ordinary ophthalmologist, of a marked personal inadequacy in understanding the niceties of vascular dynamics, quite apart from ocular dynamics, and one looks forward to more collaborative work between ophthalmologists and general physicians in this difficult area.

REDMOND SMITH

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3 Cole MD, Dodson PM, Hendeles S. Medical conditions underlying retinal vein occlusion in patients with glaucoma or ocular hypertension *Br J Ophthalmol* 1989, 73: 693–8
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ORIGINAL ARTICLES

# Latency-associated transcripts in corneas and ganglia of HSV-1 infected rabbits

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**Abstract**

**Herpes simplex virus (HSV) establishes latent infection in the sensory neuron and possibly in non-neuronal tissue, particularly the cornea. During latency only one region of the HSV genome is transcribed, producing RNAs known as latency associated transcripts (LAT). The gene for LAT overlaps with the HSV gene for the protein ICPO in the downstream regions of both genes. Latency can occur in the absence of LAT. This study reports the detection of ICPO/LAT and thymidine kinase (TK) gene fragments by the polymerase chain reaction in DNA extracted from the corneas and trigeminal ganglia of latently infected rabbits. Both genes were detected in four of four trigeminal ganglia tested and in three of five corneas tested. More importantly, this study reports the first detection of LAT in RNA extracted from 9% of corneas from latently infected rabbits (n=22) by the polymerase chain reaction. LAT was detected in RNA from 100% of the corresponding trigeminal ganglia (n=22). Although LAT is not essential for latency, it remains the only known molecular marker for latent HSV infections. Detection of LAT in these rabbit corneas suggests that HSV latency may occur in this non-neuronal tissue and that reactivation from non-neuronal tissue may occur at a low frequency in animals in which HSV latency has been established.**

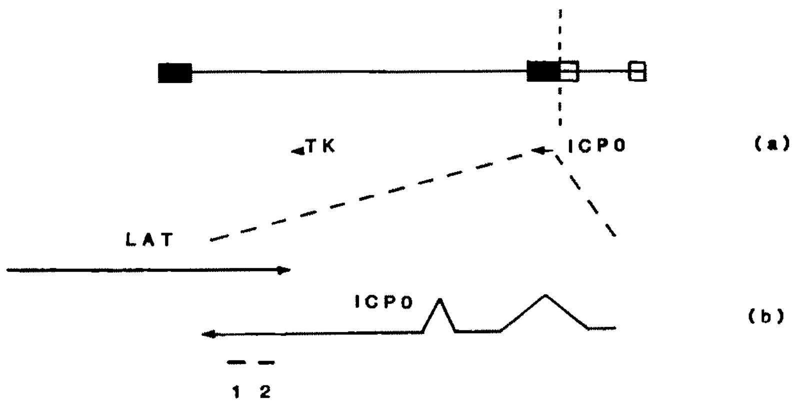

*Figure 1 (a) Prototype orientation of HSV-1 genome, showing location of TK and ICPO genes. (b) Expanded ICPO gene showing area of overlap with LAT and site of intragenic LAT/ICPO primers.*

The sensory neuron is acknowledged as the principal site for HSV latency,[1–4] but other neural tissue, specifically the autonomic ganglia, also harbour latent HSV.[5] Before a herpetic infection can be described as latent in a particular target tissue by the operational definition[6] two conditions must be met: (1) at the time the host animal is killed, cell-free infectious virus must not be detectable (the detection of cell-free infectious virus implies acute infection or reactivation); (2) virus must be detectable after a period of organ culture of the target tissue.

A latency definition based on events occurring at a molecular level does not exist. Latency-associated transcripts (LAT) were first reported in 1987.[7] This limited transcription of the HSV viral genome has been demonstrated in mice,[7 8] rabbits,[9 10] and man.[11–15] Since then LAT has been shown to be non-essential for the establishment of latency in studies using HSV-1×HSV-2 deletion mutants[16–18] in mice. Other reports suggest that LAT may facilitate reactivation from organ culture[17 18] and reactivation induced in vivo in rabbits by iontophoresis of epinephrine.[19]

With the operational definition of HSV latency, non-neuronal sites, including human,[20–22] rabbit,[23 24] and mouse[25] corneas, have been shown to support latent HSV infections. The frequency of HSV isolation from human and animal corneas is low, ranging from 11 to 30%.[20–25] These frequencies are comparable to those obtained in similar studies of mouse skin and footpads.[26 27] However, in situ hybridisation applied to human corneas by means of 'sense' and 'antisense' single-stranded RNA probes from the ICPO gene, which overlaps with LAT, failed to detect HSV transcription in human corneas.[28] Other studies using HSV probes which encompass the whole genome have detected HSV DNA by in-situ hybridisation in rabbit corneas up to day 60 post injection,[29] and HSV DNA by dot blot hybridisation in herpes infected human corneas removed at keratoplasty.[30]

Investigation of gene expression during latency is difficult, as so few cells appear to harbour latent HSV.[31] The polymerase chain reaction (PCR) is an extremely sensitive tool for the analysis of viral gene expression.[32 33] This technique has been used to detect HSV gene expression in mouse ganglia.[34 35] We now report on the use of this technique to detect HSV gene expression in the corneas and trigeminal ganglia of latently infected rabbits.

*Table 1 · Clinical history of corneas subjected to DNA extraction*

| Rabbit number | Virus strain | Antiviral treatment | Reactivation by iontophoresis | | Corneal scarring | | Killed (day PI) |
|---|---|---|---|---|---|---|---|
| | | OU | OD | OS | OD | OS | |
| MI1 | MI | ND | ND | ND | – | – | 5 |
| HSV1 | 17 Syn+ | ND | ND | ND | DU | DU | 5 |
| J67 | 17 Syn+ | ND | No | * | + | * | 85 |
| J56 | McKrae | ND | Yes | Yes | – | – | 81 |
| 1421 | McKrae | P, A | ND | ND | – | – | 41 |

Iontophoresis: Yes, virus reactivated, No, virus not reactivated. Corneal scarring +, present; –, absent. Antiviral treatment. P,=PMEA [9-(2-phosphonomethoxyethyl) adenine]; A,=acyclovir ND, not done. MI, mock-infected DU, dendritic ulcer. *J67. The cornea OS and both trigeminal ganglia were mishandled during processing and therefore unavailable for other analysis

## Materials and methods

### RABBITS AND VIRAL INOCULATION

The unscarified eyes of New Zealand white rabbits (1·5–2·5 kg) were infected with a suspension of either HSV-1 strain 17 Syn$^+$ or McKrae at $10^5$ plaque forming units (PFU) in 20 µl. Primary corneal infection was verified by slit-lamp biomicroscopic examination (SLE) between days 4 and 8 post inoculation.

When killed (days 41–147 post inoculation), the rabbits had been used in either antiviral or reactivation experiments. Rabbits in the antiviral experiments had been treated with either acyclovir or PMEA [9- (2-phosphonylmethoxyethyl)-adenine][36] during the primary infection between days 3 and 8 post inoculation. One rabbit (no 954) was an untreated control in antiviral experiments. Additional rabbits were used as mock-infected controls and acutely infected controls (sacrificed on day 5 post inoculation). The corneas were assessed clinically by slit-lamp biomicroscopic examination and preocular tear film was collected and monitored as previously described[37] to detect the presence of infectious HSV.

### PREPARATION OF NUCLEIC ACIDS FROM GANGLIA AND CORNEAS

Immediately after the rabbits were killed the corneas and trigeminal ganglia were removed aseptically and frozen in liquid nitrogen before storage at −70°C. DNA was extracted from corneas and trigeminal ganglia by standard methods.[38] For RNA extraction individual corneas were ground under liquid nitrogen, and the tissue was homogenised briefly with a probe (TEKMAR, Cincinnatti, OH) in guanidinium thiocyanate, then centrifuged on caesium chloride.[39] Homogenisation was unnecessary in the preparation of trigeminal ganglia. Samples of RNA for positive and negative PCR controls were prepared by the same method using acutely infected (sacrificed on day 5 PI) and mock-infected rabbits, respectively.

*Table 2 Clinical history of corneas subjected to RNA extraction*

| Rabbit number | Virus strain | Antiviral treatment | Reactivation by iontophoresis | | Corneal scarring | | Killed (day PI) |
|---|---|---|---|---|---|---|---|
| | | OU | OD | OS | OD | OS | |
| MI2* | MI | ND | ND | ND | – | – | 5 |
| HSV2* | 17 Syn+ | ND | ND | ND | DU | DU | 5 |
| H67 | 17 Syn+ | ND | Yes | Yes | – | – | 145 |
| H59 | 17 Syn+ | ND | No | No | – | – | 143 |
| 1414 | McKrae | P | ND | ND | – | – | 41 |
| 1419 | McKrae | P | ND | ND | – | – | 41 |
| 954 | McKrae | ND | ND | ND | + | + | 41 |
| 1409 | McKrae | A | ND | ND | + | – | 41 |
| J52 | McKrae | ND | No | Yes | – | – | 94 |
| J53 | McKrae | ND | Yes | No | + | + | 94 |
| J41 | McKrae | ND | Yes | Yes | – | – | 147 |
| J45 | McKrae | ND | Yes | Yes | – | – | 147 |
| J47 | McKrae | ND | Yes | Yes | – | – | 147 |

Iontophoresis: Yes, virus reactivated; No, virus not reactivated. Corneal scarring +, present; –, absent Antiviral treatment: P,=PMEA [9-(2-phosphonomethoxyethyl) adenine], A,=acyclovir. ND, not done. MI, mock-infected. DU, dendritic ulcer. *Controls.

### DNA POLYMERASE CHAIN REACTION (PCR)

The method of Saiki *et al* was used.[33] Briefly, the polymerase chain reaction has three steps which are repeated in sequence for many cycles: denaturation, in which double-stranded DNA is melted to single strands; annealing, in which primers locate and adhere to the complementary single-stranded DNA template; and extension, in which dNTPs are polymerised, complementing the bases on the single-stranded DNA template. This primer extension phase is mediated by the heat stable Taq DNA polymerase. Each cycle theoretically doubles the number of copies of template DNA.

Molecular weight standards were the Hae III digest of øX174 RF DNA. The gels were prepared and used as previously described.[34 35] They were stained with ethidium bromide and observed under UV light. Figures 2 and 3 represent prints of the negative of the gel.

### RNA PCR

RNA was converted to single stranded DNA (cDNA) by means of reverse transcriptase and the addition of an appropriate primer.[35] cDNA synthesis occurs only if the initial RNA sample is complementary to the primer. The polymerase chain reaction thus identifies which RNA strand serves as the template for RNA transcription. This reaction product was used as a cDNA template in the PCR.

### DESIGN OF PRIMERS

Oligonucleotide primers (20 bases) have been synthesised and previously described[34 35] for three HSV genes: the thymidine kinase (TK), LAT, and ICPO genes (Fig 1). The TK and ICPO/LAT fragments amplified are 110 and 195 base pairs, respectively. The LAT and ICPO genes are partly complementary at the three prime ends. Selective addition of the downstream primer ensures cDNA synthesis when the initial RNA sample is complementary to the DNA primer added. Because the LAT and ICPO genes are complementary at the three prime ends, a positive result may be obtained if contaminating ICPO DNA is present. To eliminate the possibility of a false positive arising from contaminating ICPO DNA in this manner, polymerase chain reactions were also performed on RNA which had not been processed to cDNA.

### EXPERIMENTAL DESIGN

Five corneas from three rabbits with latent HSV-1 and four trigeminal ganglia from two of these

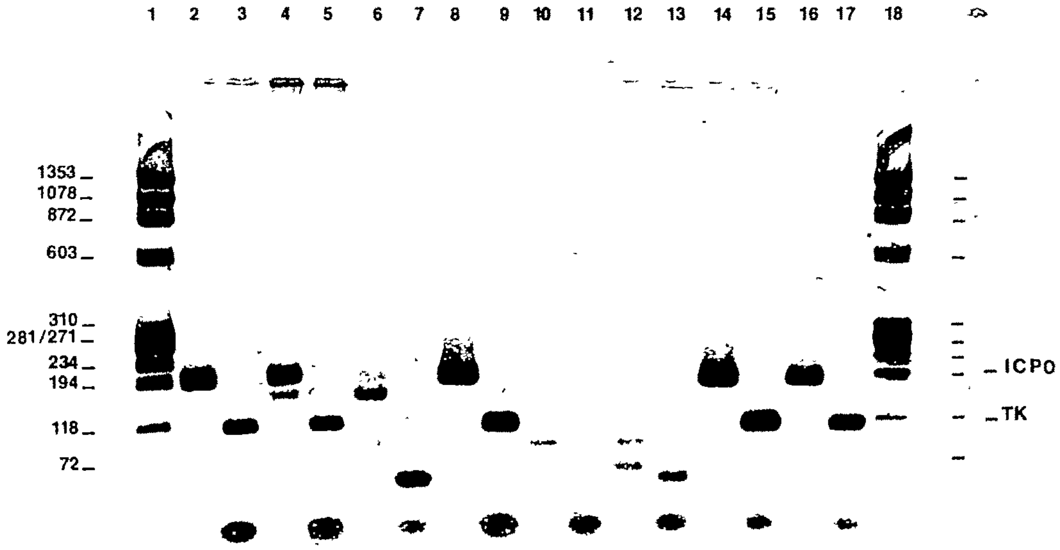

*Figure 2 DNA PCR. Lanes 1, 18 marker $\phi$X174 RF DNA; lanes 2, 3 right cornea 1421; lanes 4, 5 right trigeminal ganglion 1421; lanes 6, 7 right cornea J56; lanes 8, 9 right trigeminal ganglion J56; lanes 10, 11 mock-infected cornea; lanes 12, 13 mock-infected trigeminal ganglion; lanes 14, 15 acutely infected cornea; lanes 16, 17 acutely infected trigeminal ganglion. Even numbered lanes (except 18) had ICPO/LAT primers added during the PCR reaction; product 195 bp. Odd numbered lanes (except 1) had TK primers added during the PCR reaction; product 110 bp.*

rabbits were used for DNA analysis (Table 1). Twenty-two corneas and 22 trigeminal ganglia from 11 rabbits with latent HSV-1 were subjected to RNA extraction (Table 2). DNA and RNA were extracted from the corneas and trigeminal ganglia of mock-infected and HSV-1 acutely infected rabbits and used as controls (Table 1, 2).

## Results

### OCULAR SWABBING AND SLIT-LAMP EXAMINATION AT DEATH

With the exception of the acutely infected rabbits, no rabbit had an active herpetic infection when killed as shown by epithelial ulceration. HSV was detected only in the tear film of the acutely infected control rabbits immediately before death and not in the tear film of any of the HSV-1 latent rabbits, which were killed between days 41 and 147 post inoculation. One of the five corneas in the group of DNA extractions had scarring in more than two quadrants. Five corneas (three rabbits) of the 22 eyes in the group of RNA extractions had dense scarring in two or more quadrants.

### DNA POLYMERASE CHAIN REACTION

With previously described intragenic primers with characterised products for the TK and ICPO genes[34, 35] and polymerase chain reaction detected HSV-1 DNA sequences for the thymidine kinase (110 bp) and ICPO genes (195 bp) in all four ganglia from latent rabbits analysed (Fig 2, lanes 4, 5, 8, 9). The corresponding trigeminal ganglion from one rabbit (J67) was not available for use in this study. With the same

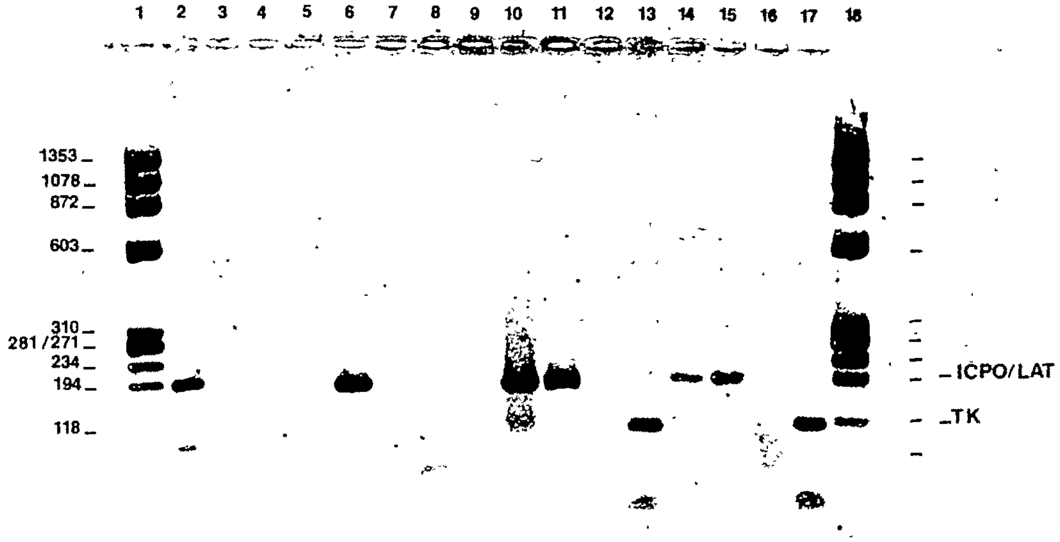

*Figure 3 Lanes 1, 18 marker $\phi$X174 RF DNA; lanes 2–5 right cornea 954, lanes 6–9 right trigeminal ganglion 954; lanes 10–13 acutely infected cornea; lanes 14–17 acutely infected trigeminal ganglion. Lanes 2, 6, 10, 14 primer 2 added during reverse transcription. Lanes 3, 7, 11, 15 primer 1 added during reverse transcription. Lanes 4, 8, 12, 16 no reverse transcription, PCR on RNA. Lanes 5, 9, 13, 17; downstream TK primer added during reverse transcription. Upstream and downstream primers were added to samples 2–17 during the PCR.*

intragenic primers the TK and ICPO genes were detected by polymerase chain reaction in three of the five corneas studied: J67 right (not shown in Fig 2); 1421 right and left. No TK or ICPO genes were detected in either cornea of rabbit J56 despite positive results from the trigeminal ganglia (Fig 2, lanes 2 and 3, 6 and 7). The PCR failed to detect HSV sequences in two mock-infected corneas and the two corresponding trigeminal ganglia (Fig 2, lanes 10–13). TK and ICPO genes were detectable by PCR in DNA extracted from both corneas and both trigeminal ganglia of an acutely infected rabbit sacrificed on day 5 post inoculation (Fig 2, lanes 14–17).

Additional bands smaller than the predicted PCR products are evident (Fig 2, lanes 4, 6, 7, 10, 12, and 13). These may represent incomplete primer extension products or an area of partial homology between the primers and the host genome. Previous sequence analysis of a 300 bp PCR product obtained with the same ICPO/LAT primers revealed homology with only the oligonucleotide primers.[35]

### RNA POLYMERASE CHAIN REACTION

LAT was detected in all 22 trigeminal ganglia from HSV-1 latent rabbits by PCR on cDNA after addition of the downstream LAT primer (Fig 3, lane 6) during the reverse transcriptase reaction. In contrast, detection of LAT in rabbit corneas after the above procedure was limited, with only two positives from 22 corneas analysed (9%) (Fig 3, lane 2). The two positive results were obtained from the same rabbit (no 954), which was killed on day 41 post inoculation. Interestingly, both corneas were scarred. The PCR performed on cDNA which had the upstream LAT primer was negative (Fig 3, lane 3). The PCR performed on the RNA sample without a reverse transcription reaction was also negative (Fig 3, lane 4). These two negative results controlled for the presence of contaminating cDNA. Thus the detection of LAT is attributable solely to the presence of antisense RNA in the extracted tissue. Similar control results were also obtained for the latently infected trigeminal ganglia (Fig 2, lanes 7, 8). In each PCR run, appropriate positive (HSV-infected) and negative (mock-infected) controls were included.

The two corneal specimens positive for LAT (no 954) were also assessed for the presence of TK transcripts using a reverse transcriptase procedure followed by PCR. TK transcripts were not detectable (Fig 3, lane 5) on two PCR assays. Four of the 22 trigeminal ganglia positive for LAT were also tested for TK transcripts with similar results – that is, no TK transcripts were detected (Fig 3, lane 9).

In contrast, in acutely infected corneas and trigeminal ganglia LAT, ICPO, and TK transcripts were detectable when the appropriate downstream primer was added during the reverse transcriptase reaction, followed by PCR (Fig 3, lanes 10, 11, 13–15, 17). The results of the polymerase chain reaction performed on RNA using upstream and downstream primer without a reverse transcriptase reaction were negative (Fig 3, lanes 12, 16), implying that contaminating DNA was absent. Reverse transcription and the PCR were also performed on DNA and RNA from mock-infected animals with negative results (data not shown).

## Discussion

The reduced frequency of viral detection in non-neuronal tissue,[20-27] compared with neuronal tissue, after organ culture raises the question, 'Is this apparent latency genuine?' Other possible explanations exist, namely, that a persistent low-grade infection is occurring or that a reactivation event has just occurred and requires virus amplification before it can be detected. Under these conditions the possibility also exists that a relatively insensitive assay system for infectious virus may yield a false negative result.

An additional problem with the concept of non-neuronal latency is reconciling the detection of infectious HSV with the detection of genomic HSV in nucleic acid studies. The nucleic acid studies detect HSV DNA at a frequency greater than the detection of infectious HSV from non-neuronal tissue during organ culture. Specifically, in-situ hybridisation studies using HSV probes which encompassed the whole genome detected HSV DNA in 100% (26 eyes) of rabbit corneas up to 60 days post inoculation, yet no infectious HSV was detected from a separate sample of the same corneas after organ culture.[29] A further study using HSV probes which encompass the whole genome detected HSV DNA by dot blot hybridisation in 50% (seven of 14 eyes) of human corneas.[30] The use of HSV DNA probes which encompass the whole genome does not distinguish between a fragment of HSV DNA and the intact whole genome being retained in the cornea. It is therefore conceivable that the whole genome was not present.

In our experiments TK and ICPO genes were detected by the polymerase chain reaction from the DNA of all ganglia analysed (4/4). The same genes were detected by PCR in three of five corneas. When the animals were killed, there was no gross evidence of an active corneal herpetic infection, and culture of ocular swabs did not yield infectious HSV. Although the absence of gross evidence and negative HSV culture do not absolutely exclude the possibility of an asymptomatic herpetic infection, the presumption was made that no acute HSV infection was present in the trigeminal ganglia and corneas.

The detection of HSV DNA in the cornea confirms previous findings with in-situ hybridisation,[29] dot blot hybridisation,[30] and PCR (E Dunkel; D Willey; personal communication). However, the presence of HSV DNA in the cornea does not imply latency. Our results of three out of five specimens (60%) with HSV DNA detected by PCR is less than the 100% reported by the in-situ hibridisation technique in rabbits[29] and similar to the 50% reported for the dot blot hybridisation technique in human corneas.[30]

Is the DNA detected by the molecular biological techniques functional, or merely a fragmented form of DNA, either incorporated or unincorporated in the host cell DNA? Current evidence suggests that viral DNA in latency may be extrachromosal in a circular episomal form[40] and associated with nucleosomes.[41]

In our RNA studies LAT was detectable in all trigeminal ganglia by PCR following a reverse transcription reaction. This confirms reports by workers using different methods.[9,11] By contrast, LAT was detectable in only two of 22 corneas (9%). Both corneas were scarred and obtained from the same rabbit (no 954), killed at day 41 post inoculation. This date represents the earliest time after inoculation when latently infected rabbits were killed. The result is similar to the reported range (11–30%) of infectious HSV detection from animal and human corneas after organ culture.[20–25] After a reverse transcription reaction, TK was not detectable by PCR in the two corneas positive for LAT (no 954) or in any of four LAT-positive trigeminal ganglia tested. This result, combined with the failure to detect ICPO after a reverse transcription reaction, suggests that small scale HSV replication (reactivation) was not occurring.

LAT has been shown to be non-essential in the establishment and maintenance of latent infection in murine sensory neurons[42] and also has been postulated to have a role in the facilitation of reactivation.[17–19] Since reactivation can arise only from a preceding latent infection, we suggest that, by inference, LAT remains a useful, if imperfect, molecular marker for latent HSV infection. The limited detection of LAT from the cornea of latently infected rabbits implies that the cornea may be a non-neuronal site where latency can occur.

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DATE OF PREPARATION: SEPTEMBER

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# Randomised double-blind trial of bromovinyldeoxyuridine (BVDU) and trifluorothymidine (TFT) in dendritic corneal ulceration

W J Power, A Benedict-Smith, M Hillery, K Brady, L M T Collum

**Abstract**

**The results of a randomised double-blind clinical trial of 0·1% bromovinyldeoxyuridine (BVDU) and 1% trifluorothymidine (TFT) in 60 patients with corneal dendritic ulceration are presented. There was no significant difference between BVDU and TFT in terms of numbers of ulcers healed (p=0·61), mean healing time (p=0·065), and cumulative healing rate (p=0·058). No serious side effects were observed, though transient stinging was recorded in five patients receiving TFT and in three patients receiving BVDU. One patient in the group treated with TFT developed a punctate epitheliopathy.**

Trifluorothymidine (TFT) has been used in the treatment of herpes simplex keratitis since the early 1970s, and its efficacy is well established. Studies have shown that, when TFT eyedrops are used five times daily, up to 97% of dendritic ulcers will be healed within two weeks.[1] It has two modes of action. It directly inhibits the de novo synthesis of thymidine and also acts as a substitute thymidine analogue on DNA polymerase.[2] Epithelial toxicity has been described in association with TFT use, but is seen infrequently.[3]

Bromovinyldeoxyuridine (BVDU) is a new, promising antiviral agent. It is a thymidine analogue[4] with a very high potency and selectivity against herpes simplex virus type I (HSV-1) and varicella zoster virus (VZV). BVDU inhibits the replication of HSV I[5-8] and VZV[9] at concentrations of 0·001–0·01 mg/l, whereas cell toxicity is observed only at drug concentrations of 50–100 mg/l. This highly selective antiherpes activity is due to its phosphorylation by HSV-1 and VZV encoded thymidine kinase.[10] Once converted to the triphosphate form, BVDU inhibits viral DNA polymerase. In this activated triphosphate form it possesses a much greater affinity for viral DNA polymerase[11] than for host cellular DNA polymerases. HSV-2 encoded thymidine kinase is less efficient in phosphorylating BVDU, and consequently the drug is less effective against HSV-2.[10] BVDU is also inactive against thymidine kinase deficient (TK–) mutants of HSV.[10]

Animal studies have shown topical BVDU to be significantly better than IDU in promoting the healing of epithelial keratitis[12 13] and superior to TFT in suppressing the development of HSV-1 stromal disease.[14]

Short term[15 16] and long term[17] clinical studies have shown that BVDU is a safe and effective agent in the treatment of HSV-1 dendritic, geographic, and stromal keratitis. However, so far no randomised clinical trials have been reported comparing it with the currently available antiviral agents.

We report the results of a randomised double-blind comparative study of 0·1% BVDU and 1% TFT eyedrops in patients with corneal dendritic ulceration.

## Materials and methods

Patients with a clinical diagnosis of dendritic corneal ulceration were included in the study if they could attend regularly for follow up. Informed consent was obtained from each patient or from the parents in the case of children. Uniocular patients, or those who had received local antiviral treatment or steroids during the preceding two months, were excluded. At all visits a full ocular examination was carried out. Patients were seen as often as clinically necessary but at least twice weekly during treatment.

The trial was conducted in a double-blind randomised fashion. Treatment consisted of either BVDU 0·1% or TFT 1·0% ophthalmic drops, which were packaged in identical bottles and prescribed five times daily. If no improvement occurred after four days, or if the condition deteriorated, the patient was withdrawn from the study and was treated with 3% acyclovir ophthalmic ointment. Healing was deemed to have been achieved when there was no longer any fluorescein uptake. Symptoms of pain, photophobia, lacrimation, and grittiness were scored at each visit on a four point scale (0=absent, 1=mild, 2=moderate, 3=severe). A record was made of any adverse events attributable to the treatment. All patients have subsequently been followed up and any recurrences recorded.

## Results

Sixty patients were entered into the study. Thirty received TFT and thirty received BVDU. One patient in the BVDU group was lost to follow-up and was not included in the analysis. There was no significant difference between the two groups with respect to sex and age distribution, duration and severity of symptoms before treatment, and ulcer size (Table 1).

In the TFT group 29 of the 30 ulcers healed while in the BVDU group, 27 of the 29 healed. This difference was not statistically significant (p=0·61, Fisher's exact test).

The number of days taken to heal in patients

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*Table 1 Comparison of BVDU and TFT treated groups at presentation*

| | *BVDU* | *TFT* |
|---|---|---|
| Number of patients treated | 30 | 30 |
| Number (%) female | 23 (77%) | 20 (67%) |
| Age range (yr) | 15–72 | 9–66 |
| Average age (yr) | 43·3 | 47·1 |
| *Duration of symptoms before treatment* | | |
| <1 Week | 24 | 23 |
| 1–3 Weeks | 6 | 7 |
| >3 Weeks | 0 | 0 |
| *Average severity of symptoms at presentation (range 0–3)* | | |
| Pain | 1·5 | 1·6 |
| Photophobia | 2·1 | 2·3 |
| Lacrimation | 1·6 | 1·7 |
| Grittiness | 1·2 | 1·3 |
| *Approximate ulcer size at presentation (mm)* | | |
| Range | 1–8 | 2–8 |
| Average | 4·1 | 4·1 |

*Table 3 Patients treated with BVDU (total 30)*

| *Patient's sex and age (yr)* | *Number of days to healing* | *Side effects* | *Follow-up (months)* |
|---|---|---|---|
| M 56 | 13 | None | 1 |
| M 52 | 5 | None | 1 |
| M 50 | 4 | None | 1 |
| M 34 | 8 | None | 2 |
| M 72 | 4 | None | 2 |
| M 30 | 9 | None | 3 |
| M 32 | 12 | None | 3 |
| M 64 | 7 | None | 3 |
| M 30 | 12 | None | 4 |
| M 69 | 7 | None | 4 |
| M 20 | 7 | None | 4 |
| F 47 | 10 | None | 5 |
| M 43 | 8 | None | 5 |
| M 72 | 14 | None | 6 |
| M 37 | Lost to follow-up | – | 8 |
| M28 | 8 | None | 8 |
| F 33 | 5 | None | 9 |
| F 71 | 7 | None | 10 |
| F51 | Withdrawn | None | 10 |
| M 19 | 6 | None | 11 |
| F 49 | 7 | Stinging | 11 |
| F 64 | 7 | None | 11 |
| M 24 | 5 | None | 11 |
| M 29 | 9 | None | 11 |
| M 33 | 13 | None | 11 |
| F 15 | Withdrawn | None | 12 |
| M 53 | 12 | None | 17 |
| M 30 | 11 | Stinging | 18 |
| M 58 | 14 | Stinging | 19 |
| M 33 | 7 | None | 19 |

treated with TFT ranged from 4 to 12 days (average 7·2 days), compared with 4 to 14 days (average 8·5 days) for patients treated with BVDU. This difference between the mean healing time in the two groups was not statistically significant (p=0·065, Student's *t* test).

The cumulative rate of healing for both treatment groups is shown in Fig 1. Although patients treated with TFT appeared to heal more quickly, the difference between the two groups was not significant (p=0·058, Mantel-Cox test).

Symptoms of pain, photophobia, lacrimation, and grittiness resolved within 10 days in all except two patients, one in each group. The resolution time for each of the symptoms was similar in both groups (Table 2).

Side effects were seen infrequently. Stinging on initial application of the drops was noted by three patients in the BVDU group and in five who were treated with TFT. This settled in all patients within a few days of beginning treatment. One patient in the TFT group developed a punctate epitheliopathy, which resolved within three days after the patient discontinued treatment when the ulcer had healed. There was no evidence of epithelial toxicity in any of the patients treated with BVDU. Summaries of patient data and side effects are given in Tables 3 and 4.

Patients in the study continue to be monitored. The mean duration of follow-up in the TFT group was 7·9 months and in the BVDU group 6·8 months. So far there has been one recurrence in each.

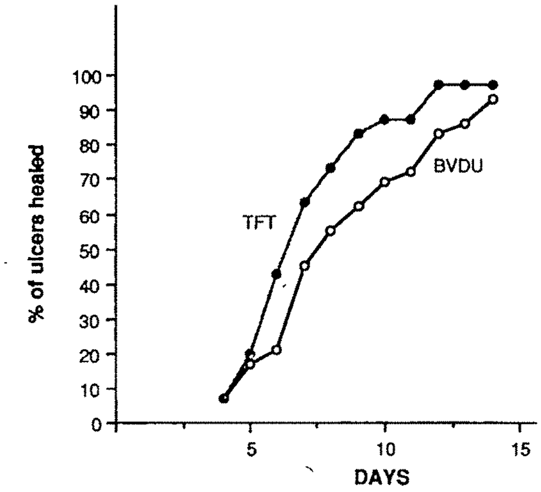

*Figure 1 Cumulative frequency distribution of time to heal dendritic corneal ulcers.*

*Table 2 Resolution of symptoms in patients receiving BVDU and TFT*

| | *Number of days to resolve* | |
|---|---|---|
| *Symptom* | *BVDU* | *TFT* |
| Pain | 6·6 | 6·7 |
| Photophobia | 7·4 | 7·8 |
| Lacrimation | 6·8 | 7·0 |
| Grittiness | 6 4 | 6·4 |

## Discussion

BVDU is a selective antiviral agent. Like acyclovir it must be phosphorylated by viral thymidine kinase to become active. Acyclovir, probably the most studied of the selective agents, has been shown to be effective in the treatment of HSV epithelial[18 19] and stromal disease[20] with minimal toxicity. However, unlike acyclovir, BVDU has minimal activity against HSV-2. This is important to remember, as HSV-2 infections, though uncommon,[21] do occur in the cornea and could account for an occasional treatment failure. Cultures may therefore be indicated in selected cases.

*Table 4 Patients treated with TFT (total 30)*

| *Patient's sex and age (yr)* | *Number of days to healing* | *Side effects* | *Follow-up (months)* |
|---|---|---|---|
| F 60 | 10 | None | 1 |
| M 59 | 12 | Stinging | 2 |
| M 58 | 6 | None | 2 |
| M 57 | 7 | Stinging | 2 |
| M 55 | 9 | None | 2 |
| M 54 | Withdrawn | None | 3 |
| M 53 | 12 | None | 3 |
| F 48 | 6 | None | 3 |
| F 25 | 8 | None | 4 |
| M 44 | 9 | None | 4 |
| F 66 | 6 | None | 4 |
| M 48 | 6 | Punctate epitheliopathy | 5 |
| M 55 | 4 | None | 5 |
| F 39 | 7 | None | 5 |
| F 46 | 6 | None | 5 |
| M 33 | 6 | None | 5 |
| F 39 | 12 | None | 8 |
| M 39 | 7 | None | 8 |
| M 42 | 7 | None | 8 |
| F 58 | 5 | None | 8 |
| F 9 | 5 | None | 8 |
| F 66 | 7 | Stinging | 8 |
| M 57 | 9 | None | 9 |
| M 25 | 5 | None | 9 |
| M 55 | 5 | Stinging | 10 |
| M 62 | 8 | Stinging | 10 |
| M 53 | 6 | None | 10 |
| M 56 | 7 | None | 17 |
| M 31 | 4 | None | 18 |
| M 21 | 8 | None | 19 |

The average healing time of 8·5 days with BVDU in this present study is similar to the healing time (8·6 days) obtained in a large series of patients in a recent open label study.[17] However, in our study BVDU 0·1% was prescribed five times daily, as compared with nine times daily in the open study. Other workers have used BVDU as a 1% ointment and achieved a healing time of 8·5 days.[22] Thus it would appear that a concentration of 0·1% BVDU eyedrops, used five times daily, achieves an optimum therapeutic effect and that higher concentrations or more frequent applications are not necessary. Except for mild transient stinging in three patients, no other side effects were noted in the BVDU treatment group.

This study shows BVDU to be a safe and effective agent in the treatment of dendritic corneal ulceration. Further studies are necessary to look at its efficacy in the treatment of stromal HSV infection.

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# Postural change of intraocular and blood pressures in ocular hypertension and low tension glaucoma

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## Abstract

**The effect of body position on the intraocular and blood pressures of normal volunteers and of patients with ocular hypertension and low tension glaucoma was studied. Changing from the sitting to the supine position increased the intraocular pressure by an average of 4·4 (SD 2·0) mm Hg in the control group, 4·0 (SD 2·0) mm Hg in the ocular hypertension group, and 4·1 (SD 1·8 mm Hg) in the low-tension glaucoma group. After 30 minutes in the supine position the intraocular pressure in normal volunteers and patients with low tension glaucoma remained stable. In contrast patients with ocular hypertension showed a further significant increase in intraocular pressure of 1·6 (SD 2·8) mm Hg ($p=0·004$). This was accompanied by an equally significant decrease in blood pressure ($p<0·001$). We believe that these are manifestations of different mechanism of intraocular pressure regulation between these groups.**

It is well recognised that a change in body position alters intraocular pressure. Several authors have reported an average rise of 2–3 mm Hg in intraocular pressure when body position is changed from sitting to supine.[1-4] Some even report changes as high as 6 mm Hg.[5 6]

In a previous report Williams, Peart, and Letley[7] studied postural changes of intraocular pressure in relation to blood pressure. They studied normal and systemic hypertensive persons and found no correlation between individual changes of systemic pressure and the magnitude of the rise in intraocular pressure in association with the change from sitting to supine. However, they discovered that patients with systemic hypertension continued to show rises in intraocular pressure even after 15 minutes in the supine position, in contrast to the normal control group in whom the intraocular pressure remained stable.

The relationship of blood pressure to blood flow is well established, and it is believed that abnormalities in autoregulation of blood flow at the optic nerve head may have an important role in pressure-induced axonal loss.[8]

We considered therefore it would be interesting to investigate the relationship between blood pressure and intraocular pressure in two clinical entities which probably represent the extremes of the glaucoma spectrum – ocular hypertension and low tension glaucoma. In the former there is an increased intraocular pressure without the resultant pathological changes of open angle glaucoma. In the latter changes associated with glaucoma are present despite apparently normal intraocular pressures.

Several studies of the postural change of intraocular pressure in glaucoma have been carried out in the past several years.[1-5 9-12] However, little has been written on ocular hypertension[10] and low tension glaucoma.[12] This paper was designed to confirm earlier reports regarding postural change of intraocular pressure in ocular hypertension and low tension glaucoma, and to investigate any possible relationship between blood pressure and intraocular pressure in these groups of patients.

## Subjects and methods

The patients with ocular hypertension and with low tension glaucoma were selected after an observation term of one year from those attending the Glaucoma Clinic of the Department of Ophthalmology, Yamanashi Medical College, from April 1988 to December 1990. Ocular hypertension was defined as an intraocular pressure over 21 mm Hg in eyes with normal visual fields, normal angles, and discs without glaucomatous cupping. Low tension glaucoma was defined as an intraocular pressure equal to or under 21 mm Hg in eyes with glaucomatous changes in the visual fields and optic discs. No patients received any medication prior to or during the examination period.

Normal controls included normal volunteers and patients selected from the general clinics. These patients had either incipient cataract or refractive error only, and no other systemic abnormality. None of the controls was having any medication that is known to influence intraocular pressures.

An Alcon Pneumatonograph (Alcon Laboratories, Fort Worth, Texas) was used to measure the intraocular pressure in both the sitting and supine positions. Prior to use, the pneumatonograph was tested and calibrated against a Silastic membrane and hydrostatic pressure before every reading. In order to confirm the stability of intraocular pressure measurements calibrations were carried out with the pneumatonograph tip in both the horizontal and vertical positions. Briefly, at a preset pressure measurements were made with the pneumatonograph tip in the horizontal position. Thereafter, while the same pressure setting was maintained in the manometer, the pneumatonograph tip was shifted to the vertical position, and 10 consecutive measurements were made. Calibrations were made at pressure increments of 5 mm Hg, starting with an initial pressure of 5 mm Hg, up to 40 mm Hg.

For the actual measurements each subject was asked to sit comfortably at the edge of an examining table in a quiet room for 10 minutes. A topical anaesthetic was instilled into both eyes,

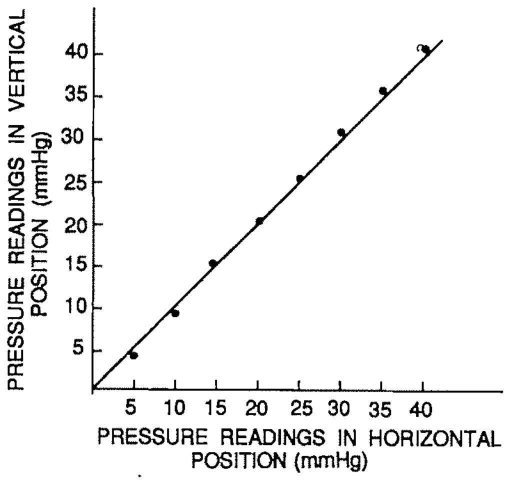

*Figure 1 Correlation between intraocular pressure readings with the pneumatonograph when the tip is in the horizontal position (horizontal axis) and in the vertical position (vertical axis). Correlation coefficient is 0·99.*

and the intraocular pressure of one eye, chosen at random, was measured while the patient was in a sitting position. Immediately after the intraocular pressure measurement the blood pressure was measured by means of a mercury sphygmomanometer. We made measurements from the left arm, making sure that the patient's arm was relaxed and that the sphygmomanometer was adjusted to a position approximating the level of the heart. Subsequently, the patient was asked to lie down and intraocular and blood pressure measurements were made in a similar manner. The intraocular pressure was measured in the same eye in which it was measured before. The patient was asked to remain in the supine position for 30 minutes, after which the intraocular and blood pressures were again measured. Finally, the patient was asked to sit up and the final measurements done. All measurements were taken by the same person (SY) in the morning, between 0900 and 1100. Three readings were taken and the mean used for the study.

The Student's *t* test for paired data was used for statistical analysis.

*Table 1 Postural change of intraocular pressure*

| | Normal control (mm Hg) | | Low tension glaucoma (mm Hg) | | Ocular hypertension (mm Hg) | |
|---|---|---|---|---|---|---|
| | Mean | (SD) | Mean | (SD) | Mean | (SD) |
| Sitting (0) | 17 5 | (3·0) | 18·4 | (2·3) | 22·5 | (3·5) |
| Supine (0) | 21·9 | (3·6*) | 22 5 | (3·2*) | 26·5 | (3·5*) |
| Supine (30) | 21·9 | (2·9) | 22 6 | (2·8) | 28·1 | (4·2†) |
| Sitting (30) | 16·7 | (2·8) | 18·2 | (2 6) | 22 3 | (3·2) |

*p<0·001 in comparison with baseline sitting intraocular pressures
†p<0·001 in comparison with baseline sitting intraocular pressure.
p=0·004 in comparison with inital intraocular pressure in supine position.

*Table 2 Postural change of systolic blood pressure*

| | Normal control (mm Hg) | | Low tension glaucoma (mm Hg) | | Ocular hypertension (mm Hg) | |
|---|---|---|---|---|---|---|
| | Mean | (SD) | Mean | (SD) | Mean | (SD) |
| Sitting (0) | 140·0 | (21 4) | 140·5 | (27·7) | 132·8 | (15·0) |
| Supine (0) | 137·6 | (19 5) | 142·5 | (30·7) | 135·0 | (14·3) |
| Supine (30) | 135·2 | (20 7) | 141·5 | (27·0) | 126·1 | (11·1*) |
| Sitting (30) | 136·2 | (22·9) | 139·5 | (28 8) | 126·9 | (11·9) |

*p<0·003 in comparison with baseline sitting blood pressure
p<0·001 in comparison with initial blood pressure in supine position

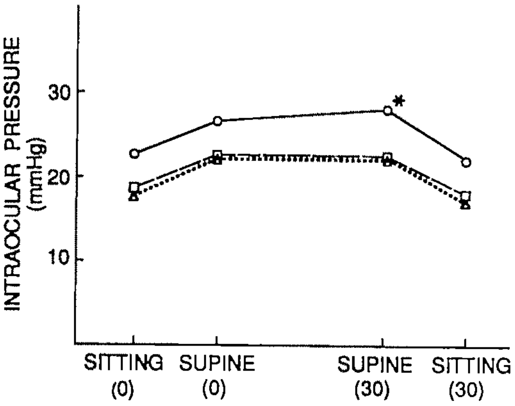

*Figure 2 Mean intraocular pressure variations in normal control eyes (triangles and dotted line), low-tension glaucoma eyes (squares and dashed line), and ocular hypertension eyes (circles and solid line). Asterisk indicates a significant increase in intraocular pressure in eyes with ocular hypertension (see text).*

## Results

The results of our calibration measurements showed that pressure readings with the pneumatonograph tip in the vertical position correlated well with readings when the pneumatonograph tip was in the horizontal position. The correlation coefficient was calculated to be 0·99 (Fig 1).

The clinical tests were carried out on a total of 16 eyes with ocular hypertension (mean age (SD) 49·4 (11·4) yr, 23 eyes with low-tension glaucoma (62·3 (11·1) yr), and 18 normal control eyes (56·5 (18·8) yr). The results are illustrated in Tables 1 and 2 and Fig 2.

The intraocular pressure increased in all subjects on assuming the supine position (Table 1 and Fig 2). There was an average rise (with SD) of 4·4 (2·0) mm Hg in normal controls, 4·0 (2·0) mm Hg in eyes with ocular hypertension, and 4·1 (1·8) mm Hg in eyes with low-tension glaucoma. The resulting intraocular pressures were significantly different in comparison with baseline readings (p<0·001).

Thereafter the pattern of intraocular pressure change associated with the sustained supine position was different in the three groups. After 30 minutes in the supine position the intraocular pressure in the control and low-tension glaucoma groups showed minimal, non-significant changes −0·05 (SD 1·97) mm Hg and 0·07 (1·48) mm Hg, respectively. On the other hand the ocular hypertension group showed a further rise of intraocular pressure of 1·6 (2·8) mm Hg (Table 1 and Fig 2). The resulting increased intraocular pressure in the ocular hypertension group was significantly different from both the baseline intraocular pressure (p<0·001) and the initial lying intraocular pressure (p=0·004). It was likewise significantly different from the intraocular pressure values of either the control or low-tension glaucoma groups (p<0·001).

The postural changes of systolic blood pressure were more variable (Table 2). In the normal controls the blood pressure decreased by 1·9 (SD 10·7) mm Hg on lying down. After the controls remained supine for 30 minutes it further declined by 2·4 (10·3) mm Hg. These changes were all non-significant.

Systolic pressures in the low-tension glaucoma group registered an initial increase of 1·7 (SD

5·2) mm Hg on lying down. After 30 minutes in the supine position the systolic pressure decreased by 1·0 (5·2) mm Hg. All changes were likewise non-significant in comparison with the baseline value or with each other.

As in the low-tension glaucoma group, systolic pressures in patients with ocular hypertension showed a slight rise of 2·0 (SD 4·2) mm Hg on lying down. However after the patients remained supine for 30 minutes, the systolic pressures dropped by 9·5 (6·4) mm Hg. The resulting blood pressure values were significantly different from both the baseline sitting systolic pressure ($p=0·003$) and the initial systolic pressure taken in the supine position ($p<0·001$).

When the patients resumed the sitting position, both intraocular and systolic blood pressures returned nearly to baseline values.

## Discussion

Intraocular pressures rose by approximately 4 mm Hg in all the groups tested. Although our results confirm earlier findings of an increase in intraocular pressure with postural change, the magnitude of the rise differs slightly from those of previous reports.[1-6, 9-12] The rise among patients with low-tension glaucoma is more easily compared, since our study showed a much lower increment than in a previous report.[12] The rise among ocular patients with hypertension is more difficult to comment on. Leonard and coworkers[10] reported a rise of 0–9 mm Hg. While they found that 85% of eyes with ocular hypertension registered increases of 0–3 mm Hg, and only 15% showed 5–9 mm Hg, they failed to give a mean figure. We can only say therefore that our findings fall within the range cited.

We believe that the quantitative change in intraocular pressure is not as significant as the rise itself, since the figures reported in literature are very variable. A review shows that, in general, intraocular pressure rises from 0·3 to 6·0 mm Hg when changing from a sitting to a supine position.[1-6, 9-12] Our results are likewise well within this range.

The fact that the magnitude of the rise in intraocular pressure in the supine position was almost identical in all the three groups is interesting. While a little surprising, we believe that they are certainly not artefactual for a number of reasons. Firstly, interobserver bias was eliminated by having only one of us do the intraocular pressure measurements all the time. This further assured a constant technique. Secondly, the examination was performed at specific times of day in order to neutralise diurnal variation. Finally, the pneumatonograph, though already a well accepted method for taking sitting and supine intraocular pressures,[1, 3, 4, 11, 12] was further calibrated in both the horizontal and vertical positions and gave an excellent correlation coefficient.

The similarity of the intraocular pressure increments between the study groups precludes the possibility of using postural change of intraocular presssure as a diagnostic tool in the diagnosis of glaucoma. It also casts doubt on any possible pathogenetic role that the postural change of intraocular pressure itself might have in glaucomatous damage to the optic nerve head. The predictive value of such postural change is even more controversial. An earlier report[12] states that patients with low-tension glaucoma showed a higher postural change than did normal people or patients with chronic open angle glaucoma, suggesting a possible predictive value for it. Our present results do not confirm this. The small number of subjects in the previous study may be a factor for this difference.

There has been speculation on the mechanism of postural intraocular pressure rise. Leonard and coworkers[10] proposed that the immediate rise in intraocular pressure on lying down may be due to a sudden increase in uveal blood flow, while the sustained rise may be due to increased aqueous production or increased outflow resistance. Krieglstein and coworkers[3] speculated that intraocular pressure rise is correlated with changes in episcleral venous pressure and ophthalmic arterial pressure. However, with our present results we tend to agree with the observation that the mechanism for the immediate as well as the persistent rise in intraocular pressure is a complex combination of factors.[9] Fundamentally, therefore, the mechanism by which intraocular pressure increases in the supine position is still largely unknown.

The pattern of intraocular pressure change after 30 minutes in the supine position is more interesting. Among the three groups only the ocular hypertension group showed a continuing and significant rise in intraocular pressure after remaining supine. A similar response has been reported earlier by Williams and coworkers,[7] though this was demonstrated in patients with systemic hypertension. Thus there might be more things in common between systemic and ocular hypertension, especially if one considers the Framingham study demonstrating an association between ocular hypertension and systemic blood pressure.[13] This will be discussed in more detail later.

The relationship of blood pressure to intraocular pressure has been extensively studied.[7, 14-17] At first glance our data do not seem to show any correlation between blood pressure and intraocular pressure, but close scrutiny reveals interesting patterns. The normal response to a postural change in our series is an initial decrease in blood pressure, followed by a further decrease while the patient is maintained in the supine position, then a rapid increase to baseline values on regaining the sitting position. On the contrary, the low-tension glaucoma group showed an initial increase, followed by a gradual decrease during the 30-minute period the patient was left lying, and a further decrease to baseline on sitting up. The response of the ocular hypertension group was the most interesting in the sense that it seems to be a mixture of the two responses. The initial response was an increase, followed by a decrease, and finally an increase towards baseline.

The initial response of the ocular hypertension group seems to parallel that of the low-tension glaucoma group. Thereafter the response closely parallels that of the normal control group. The dramatic decline of blood pressure might therefore be a delayed compensatory mechanism that would equilibrate and normalise haemodynamic as well as other unknown forces in order to approximate to the normal response. Since a sustained increase in intraocular pressure can have deleterious effects on visual function,[18] the question whether the response seen in the ocular hypertension group is responsible for maintaining the integrity of the optic nerve head despite high intraocular pressures deserves some thought.

The unusual responses of the ocular hypertension group deserves some discussion, particularly in the light of its similarity to the response of systemic hypertensive patients. Since systemic hypertension is substantially an autonomic disorder, the question of whether ocular hypertension is also an autonomic disorder should be considered.

After noting unilateral intraocular pressure rises in some ocular hypertension patients Leonard and coworkers[10] explained their observations on the basis of a local vasomotor dysfunction and speculated that the mechanism for intraocular pressure control may be located within the eye itself. They further cited Brazier's study demonstrating a change in intraocular pressure control in patients with Horner's syndrome after cervical sympathectomy. In so doing, the role of the autonomic system is introduced. The fact that intraocular pressure can be controlled with topical $\beta$ blockers further suggests that local adrenergic receptors play a part in intraocular pressure regulation. In a series of studies Clark and Mapstone have demonstrated that an autonomic defect indeed exists among ocular hypertension patients, not only locally within the eye[19, 20] but also systemically.[21] They even proposed that raised intraocular pressure may actually be a manifestation of a systemic disease.

A question arises whether low-tension glaucoma patients also have some autonomic dysfunction. This is highly probable considering the responses shown in this series. The degree of autonomic derangement might even be much more than ocular hypertension patients so as to blunt any capacity to 'recover' and approximate to the response of the normal population, resulting therefore in glaucomatous damage. Experiments are now under way in our clinics to investigate this hypothesis.

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# Plasma viscosity or erythrocyte sedimentation rate in the diagnosis of giant cell arteritis?

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## Abstract

**Plasma viscosity (PV) has replaced the erythrocyte sedimentation rate (ESR) as a routine laboratory test in many hospitals. The finding of a normal PV but raised ESR in a case of biopsy proved giant cell arteritis (GCA) cast doubt on this substitution in cases of suspected GCA. To assess the equivalence of PV and ESR in the diagnosis of this disease 40 suspected cases were prospectively investigated with both tests. The correlation between the two tests was good ($r=0{\cdot}742$, $p<0{\cdot}0001$). The substitution of one test for the other would appear to be justified in most cases of suspected GCA. In the presence of biopsy proved disease, however, the PV and ESR each produced 13·3% false negatives. These occurred both in combination with and independently of the other test showing that, when in error, the two tests may not be equivalent. In cases of doubt the performing of both PV and ESR tests together improves but does not achieve complete diagnostic accuracy. Clinical judgment based on careful assessment of all available symptoms and signs must remain the foundation of diagnosis.**

The diagnosis of giant cell arteritis (GCA) and the decision to perform artery biopsy often depends on finding a raised plasma viscosity (PV) or erythrocyte sedimentation rate (ESR). Many hospital laboratories have adopted automated measurement of PV in preference to ESR as a routine investigation. The justification for this substitution is that a close linear correlation between PV and ESR in health and in the presence of infectious, malignant, and other non-arteritic disease has been shown.[1-3] There are advantages for the laboratory in measuring plasma viscosity instead of the ESR, but to our knowledge there is no direct evidence that plasma viscosity may be substituted for ESR in the diagnosis of GCA.

The stimulus for this study was the finding of a normal plasma viscosity in a patient with a strong clinical history of GCA. The ESR, however, was found to be significantly raised, and temporal artery biopsy then confirmed the presence of GCA. These findings questioned the substitution of plasma viscosity for ESR in the routine investigation of GCA, and to clarify this situation suspected cases of this disease were prospectively investigated by both plasma viscosity and ESR.

## Material and methods

Patients suspected of having giant cell arteritis were randomly entered into the study over a 54-month period. A general medical and ophthalmic history and physical examination was performed on each.

To assess the degree of severity of the clinical findings 'Symptom points' were allotted to each patient in the following way:

*Indicators awarded two symptom points*
Temporal pain and tenderness.
Abnormal temporal vessels on palpation.
Scalp necrosis.
Tongue or jaw claudication.
Shoulder girdle/proximal muscle pain and stiffness.

*Indicators awarded one symptom point*
Headache.
Visual loss.
Amaurosis fugax or transient visual blurring.
Altitudinal field defect.
Anterior ischaemic optic neuropathy or cotton-wool spots.
Central retinal artery occlusion.
Ophthalmoplegia, diplopia, or ptosis.
Recent onset of heart failure or myocardial infarction.
Fatige, Malaise, anorexia, or weight loss.
Fever of unknown origin.
Anaemia.

Before beginning steroid therapy we collected separate samples of venous blood in potassium EDTA for measuring the ESR, PV, and full blood count. Both ESR and PV were measured only if there was a strong intention to perform a temporal artery biopsy. The ESR was measured by the Westergren method[4] and PV by the automated Coulter method.[5,6] Normal ranges of PV assumed for this study (see below) were 1·5–1·72 cP and ESR<20 mm/h for men and 25 mm/h for women. Where clinical evidence of GCA was strong, steroid therapy was begun and biopsy was performed within 24 hours. A single temporal artery biopsy was performed under lignocaine hydrochloride 2% with adrenaline tartrate 1: 200 000 local anaesthetic, and the specimen of superficial temporal artery underwent histopathological examination.

The clinical and symptomatic response to treatment with systemic steroids was recorded during the few days of inpatient care and at subsequent outpatient attendances.

## Results

A total of 40 patients suspected of having giant cell arteritis were investigated by tests for both PV and ESR, and, of these, 31 underwent temporal artery biopsy. Nine patients were not subjected to biopsy because of insufficient laboratory and clinical support of arteritis. GCA

*Table 1 Results of all biopsied cases of suspected giant cell arteritis*

| *Biopsy-positive* | | | | | | | *Biopsy-negative* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Patient no* | *PV cP* | *ESR mm/h* | *Hb g/dl* | *Age yr* | *Sex* | *Symptom points** | *Patient no* | *PV cP* | *ESR mm/h* | *Hb g/dl* | *Age yr* | *Sex* | *Symptom points** |
| 1 | 1·73† | 60 | 13·0 | 83 | F | 13 | 16† | 2·12 | 52 | 10·2 | 82 | F | 8 |
| 2 | 1·98 | 89 | 11 3 | 79 | F | 8 | 17† | 1·92 | 60 | 12·6 | 89 | F | 7 |
| 3 | 2·01 | 89 | 12·3 | 64 | F | 5 | 18 | 1·90 | 48 | 11·9 | 76 | F | 5 |
| 4 | 1·92 | 93 | 6·8 | 78 | M | 9 | 19 | 1·70 | 17 | 14·1 | 70 | M | 3 |
| 5 | 2·26 | 119 | 10·4 | 71 | F | 10 | 20 | 1·58 | 7 | 15·0 | 72 | M | 4 |
| 6 | 2 02 | 83 | 12 9 | 82 | F | 11 | 21 | 1·87 | 32 | 14·8 | 85 | F | 2 |
| 7 | 1·75† | 19† | 14·2 | 74 | F | 15 | 22 | 1·87 | 14 | 15 7 | 77 | F | 2 |
| 8 | 2·78 | 103 | 13·9 | 76 | F | 11 | 23 | 1·85 | 46 | 13 9 | 74 | M | 3 |
| 9 | 1·98 | 102 | 12·2 | 75 | M | 8 | 24 | 1·66 | 15 | 13·7 | 80 | F | 6 |
| 10 | 2·19 | 106 | 11·1 | 85 | F | 7 | 25 | 1·89 | 80 | 12·4 | 68 | F | 4 |
| 11 | 2·34 | 116 | 11·6 | 77 | F | 11 | 26 | 1·80 | 26 | 15·2 | 72 | M | 5 |
| 12 | 2·55 | 131 | 9·2 | 74 | F | 15 | 27 | 1 92 | 59 | 13·7 | 72 | F | 4 |
| 13 | 2·34 | 7† | 7 8 | 80 | F | 6 | 28 | 1 83 | 32 | 14·4 | 60 | F | 7 |
| 14 | 2 35 | 120 | 10·9 | 78 | F | 7 | 29 | 1·84 | 27 | 14·3 | 71 | F | 3 |
| 15 | 1·94 | 66 | 12·4 | 72 | F | 11 | 30 | 1·81 | 15 | 14·6 | 76 | F | 3 |
| | | | | | | | 31 | 1·87 | 41 | 13·1 | 78 | F | 7 |
| Average | 2·14 | 86·9 | 11·3 | 76·5 | | 9·8 | | 1·84 | 35·7 | 13·7 | 75·1 | | 4 7 |

*See text. †False negative result. Cases 16 and 17 suspected false negative biopsies.

was histologically confirmed in 15 (48·4%) of the 31 biopsy specimens. Definite histological proof of giant cell arteritis was missing in the remaining 16 cases (Table 1).

The ESR was plotted against PV for all 40 of cases of suspected giant cell arteritis (Fig 1). Good correlation between ESR and plasma viscosity was found, the coefficient for all cases being 0·74 ($p<0·0001$). The coefficient between PV and ESR for the 15 biopsy-positive cases was 0·46 ($p=0·082$), but when patient 13 with a low ESR related to aspirin consumption was excluded the coefficient for the biopsy positive group became 0·74 ($p=0·0024$), matching that for all 40 cases.

The symptom profile in the biopsy-negative group was less severe (average 4·7 symptom points) than in the biopsy-positive group (average 9·8 points). However, high scores in the biopsy-negative group cast considerable doubt on the biopsy results. Clinical and laboratory evidence of arteritis was so strong in cases 16 and 17 that the biopsies were taken as false negative, and steroid treatment was continued regardless. In other cases steroids were gradually tailed off according to symptoms.

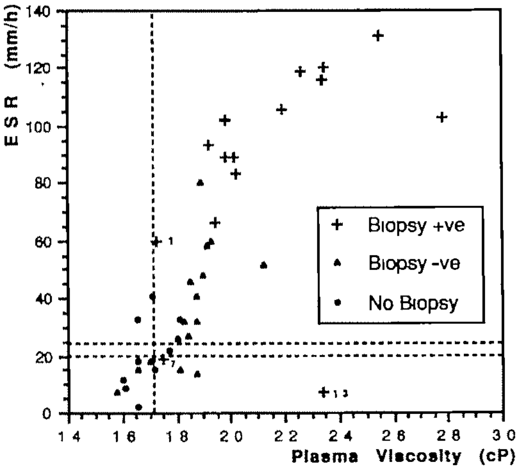

*Figure 1 Plasma viscosity plotted against ESR, with upper limits of normal shown (see text). False negative cases are numbered.*

Of the 15 biopsy proved cases only two were male. The right eye was first affected in 10 patients. One female presented with profound bilateral visual loss, both eyes being affected within a few hours of the onset of visual symptoms, her vision was reduced to counting fingers and no light perception in the right and left eyes respectively. Seven cases presented with visual field loss (lower altitudinal field loss in six cases). Transient episodes of blurring or darkening of vision were reported up to two weeks prior to onset of severe visual loss in four cases. The extraocular muscles were affected in three cases. One presented as a painful, pupil-sparing, partial third nerve palsy with ptosis without visual loss, while visual loss was associated with ptosis in one case and preceded by diplopia for two days in another. There were two cases with scalp necrosis resulting from temporal artery occlusion. Superficial temporal vessels were pulsatile, not tender, and normal to palpation in five cases (33%).

A normocytic or mildly microcytic hypochromic anaemia was found in eight (53%) of the biopsy positive cases but in only one (6%) of the biopsy negative group, case 16, which was a suspected false negative biopsy.

### BIOPSY-POSITIVE CASES WITH FALSE NEGATIVE LABORATORY RESULTS

Patient 1, with a normal PV, was suffering from Paget's disease of bone and taking etidronate disodium 200 mg daily, thyroxine 0·5 mg daily, and occasional paracetamol tablets, but no other medications. She had a normal full blood count. Patient 13, had been taking high doses of aspirin for many days for muscle pains. Her low ESR and microcytic hypochromic anaemia may have been related to this. Her plasma fibrinogen was raised at 10·3 g/l (normal 2–4 g/l). Patient 7 was taking warfarin 5 mg/day to maintain an axillo-bifemoral bypass. She had a normal plasma fibrinogen, red cell count, and red cell morphology.

### RESPONSE TO TREATMENT

Following treatment of biopsy proved cases with oral prednisolone (40–100 mg/day) the plasma viscosity returned to 1·78 cP or less within an average of eight days (range 4–14 days), with the exception of case 8, in which it remained raised for eight months despite adequate control of symptoms. Temperature returned to normal within 24 hours in the four cases with mild pyrexia. Relief from muscle pains and headache was noted within three days in eight of the biopsy-positive group and in both the suspected false negative cases and in cases 24 and 31.

The patient recovered from the partial third nerve palsy in six days. There was recovery of vision from 6/36 to 6/9 in two cases and from counting fingers at 1 m to 6/12 in another, taking three days, six days, and two months respectively. These three patients had all suffered lower altitudinal field loss preceded by 3–14 days of intermittent visual disturbances; all were left with reduced visual fields. The remaining 11 cases of visual loss, including the case of bilateral loss, had no useful recovery of vision. Case 11, who presented with a central retinal artery occlusion, died from a cerebrovascular lesion 10 days after starting systemic steroids. In the biopsy-negative group case 24 died of a myocardial infarction 18 days after her biopsy while still taking prednisolone 20 mg daily.

## Discussion

The reported average annual incidence of GCA in the white population aged over 50 years is approximately 12 per 100 000 and more than three times this in females of over 70 years.[7] The disease is not confined to whites or to those over the age of 50.[8-10] Histological evidence of GCA has been found in 5% of randomly selected necropsy cases of people over 60 who died from non-arteritic disease, and the incidence of the disease is probably much higher than reported.[11] With an increasing elderly population GCA is likely to be more frequently encountered.

A raised ESR has been central to the diagnosis of GCA. The test is cheap and requires no sophisticated equipment but has several disadvantages. It is not popular with laboratory staff because it is time-consuming and the technician must first set up the test and then return later to record the result. Blood must be used within two hours of venepuncture,[12] so individual routine tests must be performed as they present rather than stored for batch testing. The test requires a certain amount of handling of blood, with all the associated risks. The range of normal for ESR varies between laboratories and is poorly defined, as it is affected by many factors such as age, sex, drugs, red cell morphology, and cell count.[12-15] We experienced difficulty in arriving at a definitive upper limit of normal for the age group in our study. Suggested upper limits in the over 60 age group range from 14 mm/h and 20 mm/h in men and women respectively,[16] up to 40 mm/h or even 60 mm/h in cases of anaemia.[13] For the purpose of our study we took the limits to be 20 mm/h for men and 25 mm/h for women.

A normal ESR in association with GCA, as occurred in two (13%) of our biopsy proved cases, has been reported.[17-19] One of these (case 13) had been taking frequent doses of aspirin. The use of anti-inflammatory agents can rapidly reduce the ESR to within normal levels, while the PV may take many days to fall to normal levels.[5] The aches and pains associated with GCA make aspirin consumptions a likely feature of the disease which must be looked for in the drug history; if it is found, a low ESR must be interpreted with caution, and a supplementary PV test should be performed.

Many laboratories have turned to automated measurement of PV as a substitute for the ESR. The automated test requires a larger initial capital expenditure but thereafter is inexpensive, convenient and quick, and can be performed in batches of small volumes of stored blood with minimal handling.[2 5 6] Plasma viscosity is independent of factors such as age, sex, and haematocrit, and unlike the ESR it has a narrow normal range with well defined upper and lower limits[1] which vary little over many years in an individual, and a change as small as 0·05 cP may be of significance.[20] Despite this we found similar false negative rates in both PV and ESR.

Alternative blood tests to diagnose and monitor giant cell arteritis have been proposed, but none has yet stood out as a substitute for either PV or ESR, though there is some support for the use of C-reactive protein level as an adjunct to the ESR as a measure of the acute phase response.[10 17 21]

Mild normochromic or slightly hypochromic anaemia, a common finding in association with GCA,[14 22-25] was found in over half of our biopsy-positive cases was rare in the biopsy-negative group. Severe anaemia can raise the ESR and obscure the diagnosis,[4 14] but mild degrees of anaemia, in association with other evidence, should increase the level of suspicion of GCA. Suspicion must not be abandoned on finding clinically normal temporal vessels. In agreement with other studies[26-28] we found that temporal vessels in 33% of our biopsy proved cases were normal to palpation.

A definite diagnosis of GCA is reached only with a positive biopsy, though the high symptom point score of patients in this group suggests that a diagnosis might have been reached on a clinical grounds alone. Because a negative finding on biopsy does not exclude the disease,[29] a major diagnostic problem remains with the group of patients in whom biopsy confirmation is not forthcoming and suspicion persists. Repeat biopsy may produce a positive result, but the chance of obtaining a positive specimen is reduced because the patient will probably by this time have been taking steroids for a few days. Case 17 had been started on a low dose of steroids two weeks before presenting to the Eye Department and the biopsy result was considered to be false negative. We have, however, obtained a positive biopsy finding after nine days of steroid treatment from a patient outside this study.

When biopsy fails to confirm suspicions, a careful review of all relevant data must be made. The failure to find a particular feature or positive laboratory result must not be used to rule out the disease, but even weak positive findings which may not be unique to the disease, such as a marked symptomatic improvement on beginning steroids; all contribute to and strengthen the final diagnosis. If the biopsy specimen is negative and laboratory results are not far removed from normal and the index of suspicion is low, high-dose steroids should be reduced and then gradually tailed off, with a close watch being kept on the patient's symptoms.

Control of GCA by systemic steroids[30] should be monitored by symptoms rather than by the ESR or plasma viscosity.[31] Relapses are more likely within the first 18 months of treatment than later, and there is evidence to suggest that systemic steroids should be continued in all cases for at least two years. Most patients should be able to stop treatment after four to five years, though some may need to continue to take a maintenance dose of 2–3 mg of prednisolone indefinitely.[31 32] One report suggests that as many as one-third of patients with predominantly visual or neurological symptoms related to GCA may need life-long therapy.[33] Once treatment has been stopped, the patient should be warned that it may need to be urgently started again, since arteritic symptoms may return.[32]

Though a sight threatening disease, GCA in isolation does not increase mortality. In our group of 31 biopsied patients, all of which had been started on high-dose steroids, two deaths occurred while steroids were being reduced, adding weight to the report that mortality is increased in GCA in association with steroid treatment.[33] The acute and long term effects of both treating with and withholding steroids in GCA demand that a firm diagnosis is reached. Only a positive artery biopsy can provide this with certainty. Before biopsy is performed a strong presumptive diagnosis must be reached, and this may be missed if too much reliance is placed on any single clinical feature or laboratory result.

## CONCLUSIONS

The performance of biopsy in suspected cases of GCA often depends on the finding of raised PV or ESR, but either test can be normal in the presence of active disease. Both tests have similar false-negative rates, and in our study one test did not appear to be more accurate than the other. There was a close correlation between the two tests, and on this basis the routine substitution of PV for ESR in the diagnosis of giant cell arteritis would appear to be justified. However, a false-negative result can occur in either test when the other is positive, and it may be helpful to perform both tests together where a clinical suspicion exists which is not supported by one test alone. The decision to biopsy should never be made on an isolated symptom, sign, or laboratory result but must follow careful consideration of all available information.

We thank the consulting ophthalmologists at the Leicester Royal Infirmary for permission to report the findings on their patients, and Dr V E Mitchell, consultant haematologist, and Mrs B Allen, chief MLSO, and other members of the Leicester Royal Infirmary Haematology department for their assistance with this study

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# Postoperative conjunctival chemosis in cataract surgery caused by subconjunctival gentamicin injection

Milind Pande

**Abstract**

**A prospective study of 75 patients undergoing cataract surgery was conducted to identify the cause of postoperative conjunctival chemosis seen in patients with cataracts in this department. The patients were split in three groups of 25 each. Group G patients were given a subconjunctival injection of gentamicin at the end of the cataract procedure; group W patients did not receive subconjunctival gentamicin, but a cellulose wick drain was used during the procedure; and Group GW patients received a subconjunctival injection of gentamicin and a wick drain was also used. The incidence, severity, and the duration of chemosis were observed in the three groups. Chemosis was seen only in groups G and GW, and the difference between the number of patients who received gentamicin and those who did not receive gentamicin was significant ($p<0{\cdot}001$).**

Postoperative conjunctival chemosis was observed in a large proportion of our patients undergoing extracapsular cataract extraction and posterior chamber implantation procedures in the early part of 1989. This chemosis was always inclusive and invariably restricted to the lower fornicial and bulbar conjunctiva. The severity varied from a mild involvement of the lower fornicial conjunctiva to a gross chemosis extending into the upper bulbar conjunctiva with loose chemosed conjunctiva in the palpebral fissure. There was capillary closure in the conjunctival vasculature overlying the chemosed area (Fig 1).

The fact that the lower half of the conjunctiva was always involved pointed to two surgical events occurring exclusively in this area. One was the insertion of a cellulose wick to drain fluid away from the operative field during the operation, and the other was the subconjuctival injection of gentamicin at the end of the operation. This prospective study was set up to investigate whether one or both of these surgical events were giving rise to the chemosis.

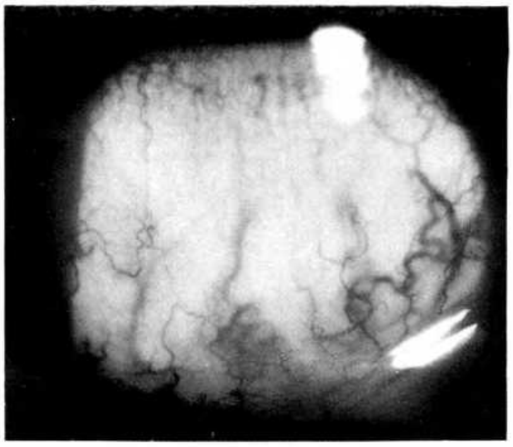

*Figure 1 Slit-lamp photograph showing capillary cl the overlying conjunctival vasculature in chemosed lo fornicial and bulbar conjunctiva.*

## Patients and methods

Patients undergoing extracapsular cataract extractions between 21 September 1989 and 19 January 1990 at the Hull Royal Infirmary were included. Their ages ranged from 44 to 88 years (mean 74·67 years). A total of 75 eyes of 75 patients were enrolled into this study.

Patients who had a past history of conjunctival chemosis, chemical burn, conjunctival trauma, keratoconjunctivitis sicca, and conjunctival lesions in the form of scarring and symblepharon were excluded from this study.

The patients were all waiting list admissions and were sequentially allocated on admission into three groups as follows. Each group consisted of 25 patients. *Group G.* Patients given a subconjunctival injection of 20 mg of gentamicin (Cidomycin) in the lower fornix at the end of surgery. Wick was not used during surgery. *Group W.* A wick was inserted into the lower fornix during surgery. Patients did not get a conjunctival injection at the end of the operation. *Group GW.* A wick and a subconjunctival injection were used as described above.

All patients underwent endocapsular or extracapsular cataract surgery under general anaesthesia by three surgeons using a manual aspiration technique. The duration of wick contact was recorded in patients of groups W and GW, and a 20 mg subconjunctival injection of gentamicin was given to patients in groups G and GW.

The conjunctival sacs of patients were examined and the presence or absence of chemosis was noted. If present the severity was noted in accordance with the following criteria: grade 1 – involvement limited to 10% to 30% of the conjunctiva; grade 2 – involvement limited to 30% to 70% to the conjunctiva; grade 3 – involvement limited to 70% to 100% of the conjunctiva.

The patients were examined daily while on the ward and the trend of chemosis noted. They were again examined for chemosis on their first postoperative clinic visit. During his examination of them the observer did not know to which groups the patients had been allocated.

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*Table 1 Incidence of chemosis in the study groups*

| | *Number of patients (%)* | | |
|---|---|---|---|
| *Group* | *Chemosis* | *No chemosis* | *Total* |
| G | 23 (92) | 2 (8) | 25 |
| W | 0 (0) | 25 (100) | 25 |
| GW | 22 (88) | 3 (12) | 25 |

*Table 2 Severity of chemosis in the study groups*

| | *Number of patients (%)* | | | | |
|---|---|---|---|---|---|
| *Group* | *Grade 1* | *Grade 2* | *Grade 3* | *No chemosis* | *Total* |
| G | 7 (28) | 13 (52) | 3 (12) | 2 (8) | 25 |
| W | 0 (0) | 0 (0) | 0 (0) | 25 (100) | 25 |
| GW | 6 (24) | 13 (52) | 3 (12) | 3 (12) | 25 |

## Results

Table 1 shows the results of the incidence of chemosis in the three groups. Twenty three (92%) of the 25 cases in group G, none of the 25 cases in group W, and 22 (88%) of the 25 cases in group GW had chemosis. The incidence of chemosis in group G and group W clearly suggests subconjunctival gentamicin as the cause of the chemosis. The difference in the incidence of chemosis in the groups in which subconjunctival gentamicin was used (groups G and GW) and the group in which no subconjunctival gentamicin was used is significant at the 0·001 level by the $\chi^2$ test.

Table 2 shows the severity of chemosis in the three groups. In group G of the 25 cases 7 (28%) had grade 1 chemosis, 13 (52%) had grade 2 chemosis, 3 (12%) had grade 3 chemosis, and 2 (8%) had no chemosis. In group GW of the 25 cases 6 (24%) had grade 1 chemosis, 13 (52%) had grade 2 chemosis, 3 (12%) had grade 3 chemosis, and 3 (12%) had no chemosis. In group W none of the 25 cases had chemosis. There is no statistically significant difference in the incidence of the three grades of chemosis between groups G and GW, indicating that the use of the wick did not influence the severity of chemosis in group GW. The conclusion is strongly supported by the fact that no chemosis was seen in any of the cases in group W, where only the wick was used. Table 3 shows the duration of chemosis seen in the 45 patients in groups G and GW who had chemosis. The duration of chemosis in these 45 patients ranged from three to seven days, average 4·64 days.

## Discussion

The cause of postoperative conjunctival chemosis in this study was the use of subconjunctival gentamicin injection at the end of the cataract operation. The cellulose wick drain did not influence the chemosis in any way.

The prophylactic use of subconjunctival gentamicin injection in cataract surgery is widespread. Gentamicin has a wide spectrum of action against common ocular pathogens, and subconjunctival injections have been shown to provide effective levels of gentamicin in the aqueous in patients undergoing cataract surgery.[1-4]

*Table 3 Duration of chemosis in days in groups G and GW*

| | *Number of patients (%)* | | | | | |
|---|---|---|---|---|---|---|
| *Group* | *3 Days* | *4 Days* | *5 days* | *6 Days* | *7 Days* | *Total* |
| G | 4 (17) | 6 (26) | 9 (39) | 1 (4) | 3 (13) | 23 |
| GW | 5 (23) | 5 (23) | 8 (36) | 2 (9) | 2 (9) | 22 |
| Total | 9 (20) | 11 (24) | 17 (38) | 3 (7) | 5 (11) | 45 |

Retinal toxicity has been reported with the use of intravitreal[5] and accidental intraocular[6] injection of gentamicin. Goulstine and Marmion in 1971[7] reported on the tolerance of a single subconjunctival injection of 20 mg gentamicin given to 10 patients at the conclusion of routine cataract surgery. They found that six of the patients had minimal conjunctival injection and chemosis 24 hours after the injection, which disappeared after a further 24 hours. They concluded that subconjunctival gentamicin is well tolerated locally and produces very little chemosis. In the present study 45 of 50 patients in the two groups (group G and GW) had chemosis. Of these 45 patients only 13 (29%) had minimal or grade 1 chemosis while 32 (71%) had more severe grade 2 or grade 3 chemosis. The chemosis lasted from three to seven days, average 4·64 days. It thus was not an insignificant problem, and in a few cases inpatient stay was longer than usual because of it.

The gentamicin preparation used in this study, gentamicin injectable 80 mg in 2 ml (Cidomycin), is widely used for the purpose of subconjunctival injections in this country. The manufacturers do not recommend the use of this preparation for subconjunctival use. Their recommended preparation for subconjunctival use in the prophylaxis prior to intraocular surgery is gentamicin sterile powder (Cidomycin), available in packs of 1 g.[8] The author believes this is not used as widely as the gentamicin injectable preparation. The difference between the two preparations is that gentamicin injectable has sodium metabisulphate, methyl hydroxybenzoate, propyl hydroxybenzoate, and disodium edetate as additives, while the recommended preparation gentamicin sterile powder has no additives.

Jenkins *et al*[9] in 1990 studied the comparative conjunctival toxicity of subconjunctival gentamicin and cefuroxime in a single-blind trial. They reported greater conjunctival toxicity in the form of hyperaemia, conjunctival oedema and capillary closure with subconjunctival gentamicin. The greater toxicity of gentamicin reported in their study may reflect the fact that the gentamicin preparation used, gentamicin injectable (Cidomycin), had the additives mentioned above, while the cefuroxime (Glaxo) preparation used in their study had no additives at all.

The possibility of the additives in the gentamicin preparation having a causative role in the conjunctival toxicity observed both in the present study and in the study by Jenkins *et al*[9] cannot be ruled out. A follow-up study to assess the role of additives in gentamicin toxicity is being conducted in this department.

The cause of postoperative conjunctival chemosis in our study was the subconjunctival injection of gentamicin given at the end of the cataract operation. The chemosis was significant in severity and duration and in some patients led to prolonged inpatient stay.

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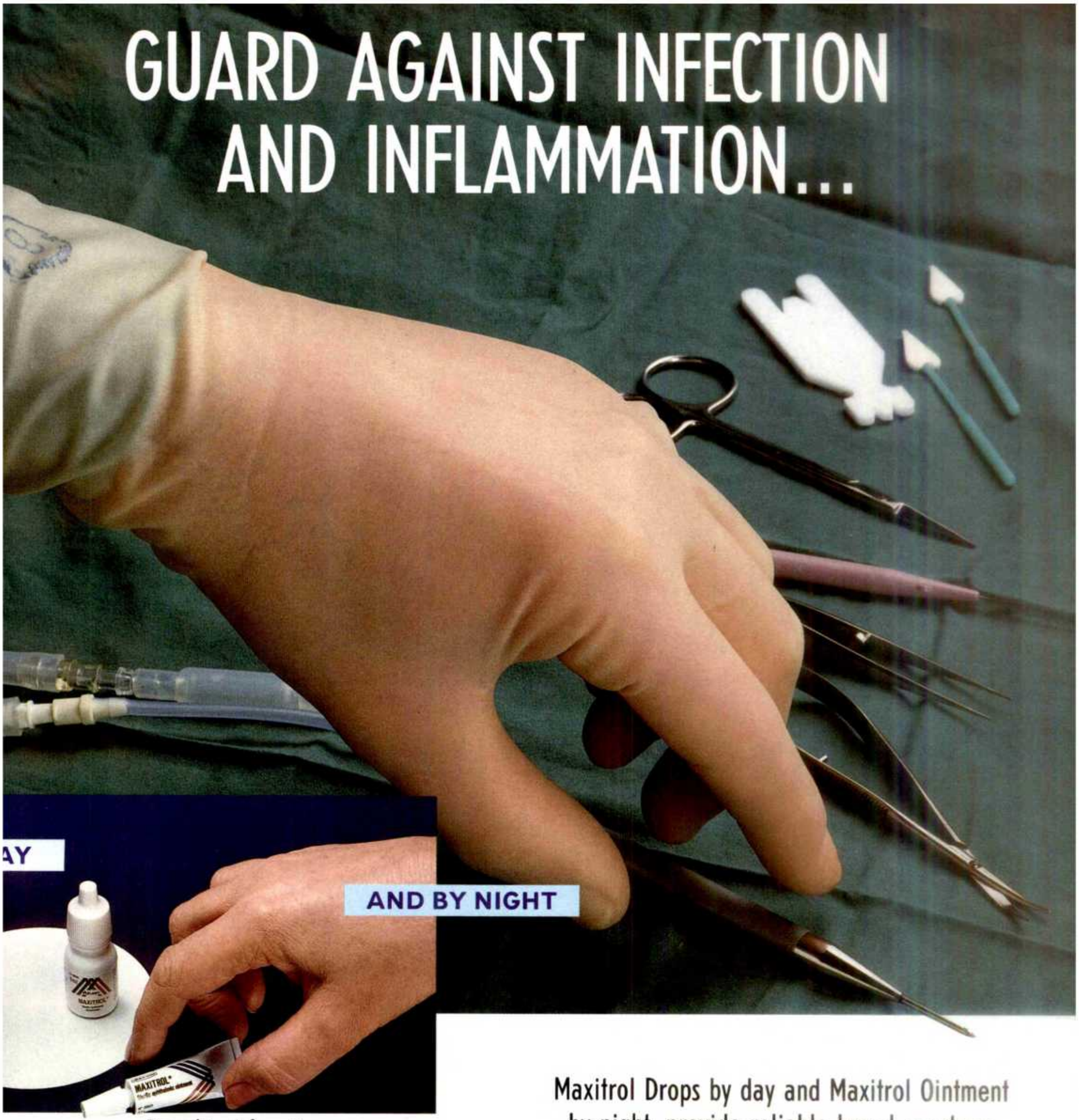
# FIFTY YEARS AGO

**Ophthalmological 'moots' in the curriculum**

It has often struck us that more use might be made in the teaching of ophthalmology of gatherings at stated intervals, say once a week, at which a subject is propounded and discussed by the students. Such meetings used to be held, we believe, in the Mayo Clinic in general surgery, and each student in turn would propose some question for discussion. Something similar to the 'Moots,' those post-prandial meetings for the cracking of legal nuts, which were revived some years ago at the Inns of Court, might be attempted at the eye hospitals in Great Britain. Such a plan would give the student confidence and would help to balance the knowledge acquired in the week in question. Ophthalmology offers plenty of subjects for serious discussion and if a wag once in a way were to ask the question whether strabismus came to England with William the Conqueror or was indigenous among the aborigines; such a light-hearted theme, incapable of proof, might help to vary the monotony. The arrangements might be left as a rule in the hands of the chief clinical assistants, and a weekly rota of attendances for the seniors, who would occupy the position of judge or arbiter, would let each man know beforehand the date of his attendance and would not add very greatly to his labours.

At the present time when the question of post-war reconstruction is being much discussed, we commend this idea to those in authority for what it is worth. On a small scale the scheme would have some affinity to the ophthalmic club which has been for many years a feature among the seniors in the profession.

Annotation in *Br J Ophthalmol* 1941; 25: 535–6.



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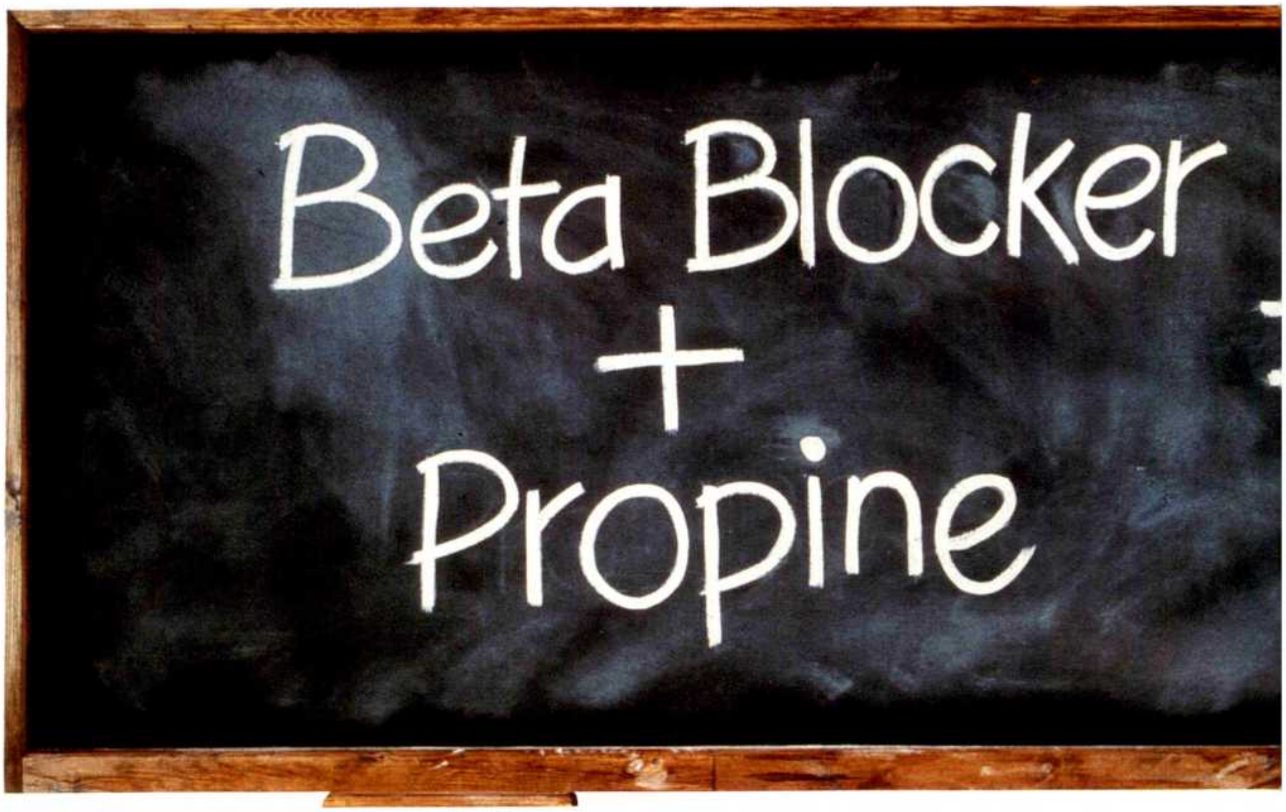

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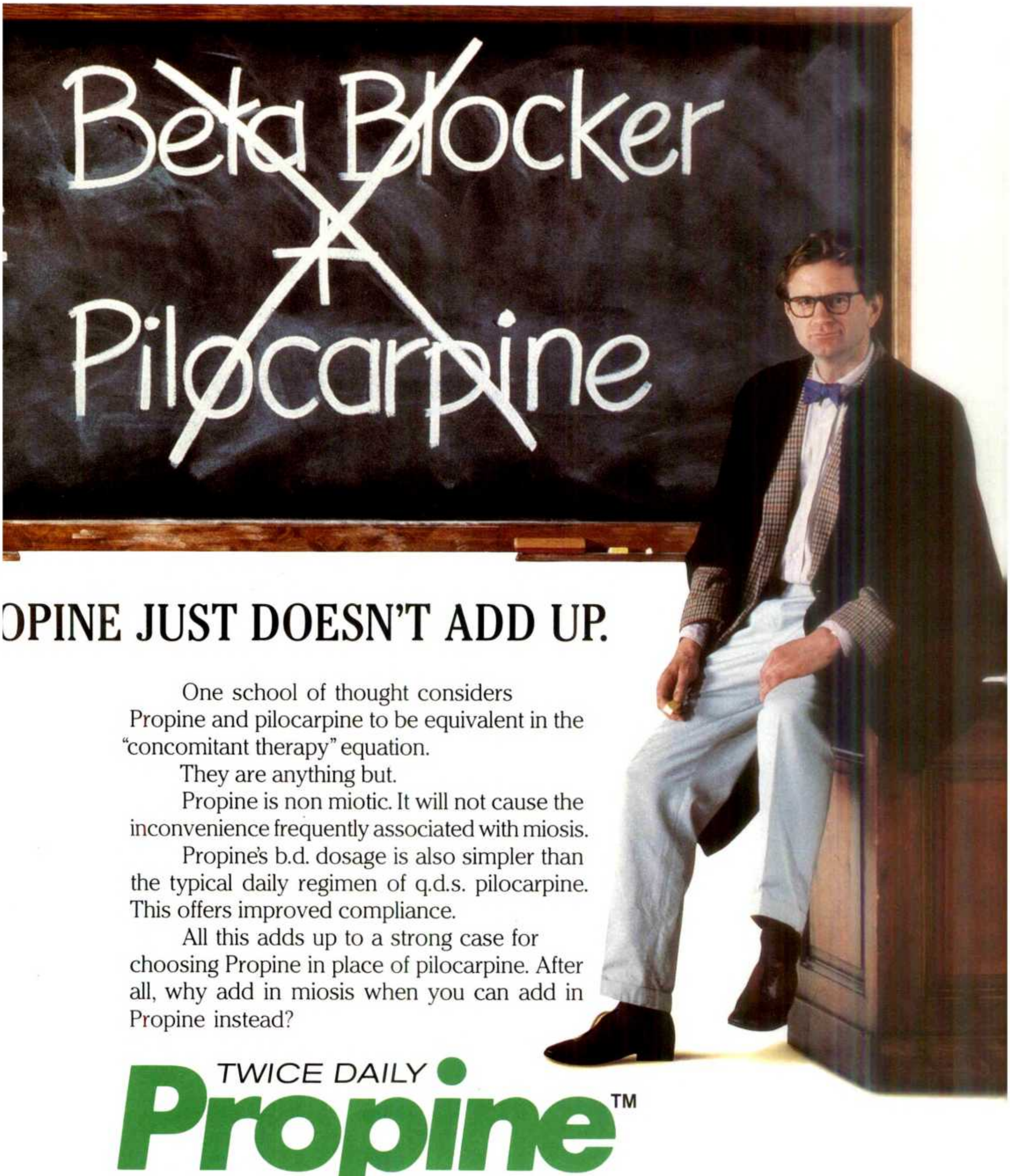

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# Should nylon corneal sutures be routinely removed?

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## Abstract

**Three groups of patients who had undergone cataract extraction through a corneal incision closed with 10/0 nylon sutures one, two, and three years previously were recalled to determine the incidence of suture related complications. Broken corneal sutures were found in 87·5% of patients after two years and 90% after three years and were causing symptoms in over half the patients. It is recommended that 10/0 nylon corneal sutures be routinely removed no later than one year after surgery.**

Opinion is divided on whether 10/0 nylon corneal sutures need to be removed following cataract surgery. Often removal of the sutures will be required to correct postoperative astigmatism. However, in those cases without significant astigmatism the authors adopted the policy of leaving the sutures in situ on the grounds of saving time in the clinic, avoiding a second refraction for the patient, and avoiding the small risk of a wound leak at the time of removal. The argument for removing all corneal sutures as a routine is that the nylon gradually degrades and some patients may suffer discomfort from the protruding ends of broken sutures.

In this study we aimed to assess the incidence of complications by reviewing patients who had undergone cataract surgery one, two, and three years previously and whose corneal sutures had been left in place.

## Material and methods

The records of patients who had undergone cataract extraction with intraocular lens implantation and whose corneal sections had been closed with 10/0 nylon during the months of April to September 1987, April to June 1988, and April to June 1989 were reviewed. In 1987 many patients still had corneoscleral incisions closed with virgin silk, and so it proved necessary to take a longer period in order to include sufficient patients with 10/0 nylon sutures. Those patients who had corneal sutures removed because of astigmatism (Table 1) were excluded. There were thus three groups of patients with corneal sutures in situ who had undergone surgery approximately one, two, and three years ago.

*Table 1 Composition of the three groups reviewed*

| | *1989 (1 year)* | *1988 (2 years)* | *1987 (3 years)* |
|---|---|---|---|
| No of patients with nylon sutures | 39 | 26 | 32 |
| No of patients who had sutures removed: | | | |
| (i) for astigmatism | 6 | 0 | 6 |
| (ii) for other reasons | 3 | 2 | 2 |
| Died | 2 | 4 | 2 |
| Unable to attend for review | 1 | 4 | 2 |
| Patients reviewed for study | 27 | 16 | 20 |

Patients were recalled by the authors and were asked about symptoms which could be related to their corneal sutures. During the examination we looked for signs of giant papillary conjunctivitis and noted the condition of the corneal sutures. We classified our findings into three groups: (i) patients with intact sutures and without symptoms; (ii) patients with broken sutures but without symptoms; (iii) patients with broken sutures and related symptoms.

## Results

Table 1 shows the composition of the three groups of patients and Table 2 summarises the findings on examination of these groups. They show that, while over 80% of patients will have intact corneal sutures at one year, this figure will have fallen to 10% by the third year postoperatively. After three years 50% of our patients had symptoms related to their broken sutures. These ranged from a minor foreign body sensation in the eye to discomfort which was sufficiently severe in two cases for the patient to be referred to the eye casualty department.

Suturing techniques changed during the three years covered by this study. In 1987 all patients had interrupted sutures; in 1988 they all had continuous sutures; while in 1989 half were continuous and half interrupted. It is worth noting that three of the four patients with broken sutures and the one patient with symptoms were in the continuous suture group.

## Discussion

The complications associated with nylon corneal sutures have been well documented[1-3] and are caused by protruding broken ends of the suture. McClellan *et al*[4] found evidence on scanning electron microscopy of surface disintegration on 10/0 nylon sutures after three months. Rijneveld *et al*[5] described the tissue reaction to nylon sutures.

In this series there were very few problems associated with nylon corneal sutures during the first year, but thereafter the incidence of symptoms increased. The patients' main complaint was of a recurrent gritty sensation. On examination the broken protruding suture ends were usually associated with marked vascularisation

*Table 2 Findings on examination*

| | *1 year* | *2 years* | *3 years* |
|---|---|---|---|
| Intact sutures | 22 (81·5%) | 2 (12·5%) | 2 (10%) |
| Broken sutures without symptoms | 4 (14·8%) | 5 (31·2%) | 8 (40%) |
| Broken sutures with symptoms | 1 (3·7%) | 9 (56·2%) | 10 (50%) |
| Giant papillary conjunctivitis with broken sutures | 0 | 1 (6·2%) | 1 (4%) |

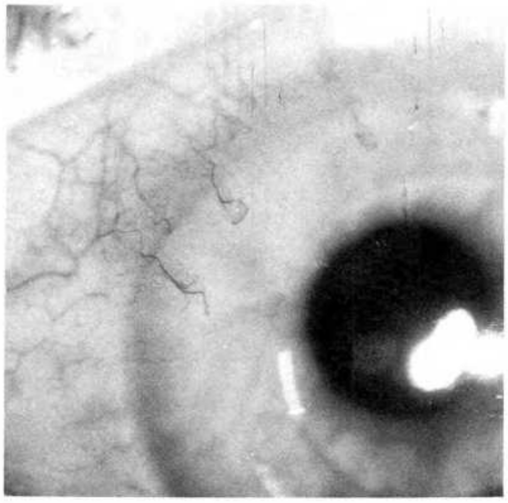

*Figure 1 Vascularisation associated with broken interrupted 10/0 nylon corneal sutures.*

(Fig 1) and often accumulation of mucus. Two patients with broken sutures had giant papillary conjunctivitis. In all cases the removal of the offending sutures resulted in rapid relief of symptoms and resolution of the signs.

These results reinforce the conclusions of Acheson and Lyons[6] that 10/0 nylon corneal sutures should be removed within 12 months of surgery. The longer that sutures are left in situ the greater the chance that they will cause symptoms. Moreover, once disintegration of the suture has begun, removal becomes progressively more difficult because the suture tends to break when it is pulled through the tissues.

We recommend that 10/0 nylon corneal sutures should be removed between three months and a year after cataract surgery.

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# Optic foraminal radiography – a redundant investigation?

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## Abstract

**A retrospective study of all plain radiographs taken of optic foramina during the six years 1984–9 inclusive, comprising a total of 318 examinations, was carried out in order to determine the role of this investigation in patients with ophthalmic disorders. All but one of the radiographs were reported as showing no abnormality. However, for this exception, review of the radiographs showed that the optic foramina were asymmetrical but fell within the normal range. This study indicates that plain radiographs of the optic foramina have little or no useful function. Abandoning the use of these views as a routine will result both in a reduction in radiation hazard and in considerable financial saving.**

Since 1924, when views of the optic foramina were first described,[1] many ophthalmologists have considered plain radiographs of the optic foramina to be an essential part of the radiological examination of the ophthalmic patient.[2] Optic nerve glioma,[3] meningioma,[4] neurofibroma,[5] and ophthalmic artery aneurysm[6] are all known to produce enlargement of the optic canal. Bony abnormalities of the optic canal are seen in Paget's disease,[7] fibrous dysplasia,[7] metastases, and trauma.[8]

The optimal positioning of the head required to obtain these views is complicated, time consuming, and requires skilled staff. Repeat views are often required to obtain satisfactory results. The radiation dose is 1–2 cGy,[9] and the cost in our centre of each examination is £35. Computed tomography (CT) and magnetic resonance imaging (MRI) produce images of very high quality, and neurologists and neuro-ophthalmologists rarely rely on plain radiographs.[10] In a recent study not one of 174 consecutive optic foraminal views was found to contribute significantly to patient management.[11] We have reviewed all the optic foraminal views taken during a six-year period in order to determine the role (if any) of plain radiographs of the optic foramina in patient management in general ophthalmic practice.

*Table 1 Indications for optic foraminal view requests*

| *Indication* | *Number* | *%* |
|---|---|---|
| Visual disturbance | 140 | 44 |
| Optic atrophy | 51 | 16 |
| Pain/headache | 35 | 11 |
| Cupped/swollen discs | 25 | 8 |
| Proptosis | 16 | 5 |
| Low tension glaucoma | 13 | 4 |
| Trauma | 10 | 3 |
| Others | 28 | 9 |
| Total | 318 | 100 |

## Material and methods

A retrospective audit was performed on all requests to the *x* ray Department of the Western Infirmary, Glasgow, for *x* rays of optic foramina over the six years 1984–9 inclusive. This department provides a radiological service for the Eye Infirmary, Glasgow, and the Tennent Institute of Ophthalmology. During the period of study all requests had been accepted without radiological vetting. The clinical indications for this examination were recorded. The result of each examination and the findings of any other imaging procedures carried out on each patient were noted. The numbers of requests for each of the years studied were determined.

## Results

A total of 318 radiological investigations were requested during the study period. All requests came from ophthalmologists. The clinical indications stated on the request cards are summarised in Table 1. Optic foraminal views alone were requested in seven cases (2%). Two hundred and ninety-two (92%) of the cards requested radiographs of the skull in addition to views of the optic foramina. Requests were received for *x* rays of the orbits and optic foramina in 17 cases (5%) and for paranasal sinuses and optic foramina in two cases (0·6%).

Nine (2·8%) of the optic foraminal views had been regarded as suboptimal for diagnosis, largely on account of excessive pneumatisation of the adjacent air sinuses. Asymmetry of the optic foramina was observed in 19 (6%) examinations, but these were deemed to have fallen within normal limits. Not one of the 318 examination of the optic foramina was considered abnormal. However, in 19 of the 292 (6%) lateral skull views which were obtained an abnormal pituitary fossa was described, but subsequent evaluation by computed tomography demonstrated a pituitary mass in only one of these cases. Other abnormalities of the skull radiographs were deemed to be incidental to the ophthalmic problem, for example, frontal mucocoele and pansinusitis. Five of the 17 orbital radiographs were abnormal. Computed tomography confirmed an orbital soft tissue mass in one case, and incidentally an aneurysm of the anterior communicating artery was identified in one other. Pansinusitis was present in one of the two examinations of the paranasal sinuses. Figure 1 shows that during the six-year period there was a significant reduction in the number for requests of optic foraminal views.

## Discussion

None of 318 optic foraminal views requested

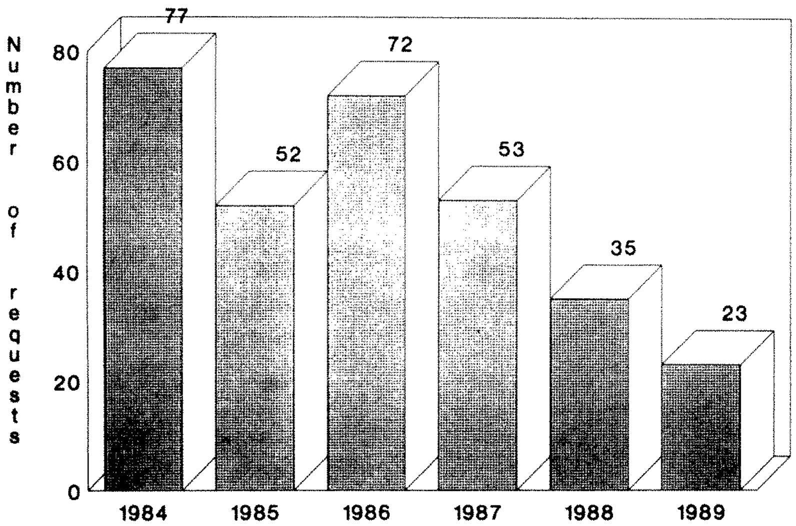

*Figure 1 Number of optic foraminal views requested during each year between 1984 and 1989.*

provided useful diagnostic information. Even when the additional views of the skull, orbits, and sinuses are considered, in the majority of cases these *x* rays provided little or no diagnostic information. The single case in which a pituitary tumour was identified had shown clinical evidence of bitemporal hemianopia, and a CT or MR examination would now be considered the principal investigation of choice in such a case. The falling number of requests for optic foraminal views during the study period indicates that clinicians are recognising the futility of this investigation when compressive optic neuropathy is suspected.

Visual loss in one eye due to an isolated optic canal lesion without concomitant manifest pathology is extremely rare.[12] In a prospective study of 174 consecutive patients Moseley[11] identified seven cases in which the optical canal views were interpreted as definitively or equivocally abnormal, but in no case were these views deemed to contribute to patient management. It has been argued that tomographic studies of the optic canal may be indicated in the rare case of suspected nerve meningioma which has not been identified by means of CT[13] or nowadays magnetic resonance imaging.

In the present study there was one false positive investigation, but there were no true positive identifications of pathology out of 318 examinations. Our results confirm those of Moseley[11] and indicate that there is little or no place for optic foraminal views in current ophthalmic practice except perhaps for cases in which pathology of bone is thought to be resulting in optic nerve compression.

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*British Journal of Ophthalmology*, 1991, 75, 667–670

# Prosthesis motility with and without intraorbital implants in the anophthalmic socket

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## Abstract

**Ocular prosthesis motility was measured and compared in 15 patients with a primary baseball implant after enucleation of an eye, in 11 patients with a secondary baseball implant, in 12 patients with an Allen implant, and in 11 patients without any intraorbital implant. In all patients a noticeable lag of movement of the prosthetic eye was measured: in the extreme directions of gaze the excursions of the prosthesis were far less in comparison with the contralateral normal eye. For normal eye movement round the primary position of gaze, however, the prosthesis motility in the primary baseball and Allen implant group appeared to be sufficient to give a lifelike appearance. The average motility of the prostheses in these two groups did not differ. The motility in the secondary baseball group and in the group without an implant was evidently worse. In the last group the prosthesis motility was most impaired. We conclude that the insertion of an implant, even when inserted some time after the enucleation (a secondary implant), improves the motility of the prosthesis markedly. We recommend the primary baseball implant as the correction of choice after enucleation.**

The cosmetic disfigurements which arise after enucleation of an eye include enophthalmos, retraction of the upper eyelid, deepening of the superior sulcus, backward tilt of the prosthesis, and stretching of the lower eyelid.[1] These symptoms, summarised in 'the postenucleation socket syndrome,' may arise separately or in combination and vary in severity. To regain a normal appearance after the enucleation they should be prevented and/or treated. This is best accomplished by substitution of the orbital volume loss (6–7 ml) with an adequate intraorbital implant.

Motility of the artificial eye is another important factor which contributes to the normal appearance of the anophthalmic orbit. Because a certain amount of prosthesis motility is a prerequisite for a lifelike aspect of the anophthalmic socket, we studied the motility in a series of patients consulting the ocularist at the Orbital Centre. This series comprises 15 patients with a primary and 11 patients with a secondary baseball implant, 12 patients with an Allen implant, and 11 patients without an implant. The prosthesis motility in these patients was measured and compared.

## Patients and methods

In a group of 49 consecutive patients who visited the ocularist (EG) after enucleation of an eye for various reasons the motility of the ocular prosthesis was evaluated. All the patients had an optimal fitting prosthesis from the ocularist's point of view. Fifteen patients had a primary baseball implant, 11 a secondary baseball implant, 12 an Allen implant, and 11 patients had no intraorbital implant. The baseball implants[2] were 18 mm acrylic balls covered with donor sclera. They were all inserted in our centre according to the primary and secondary implantation technique as described by Collin.[3] In the case of primary implantations the ball covered by sclera was placed in Tenon's space. The four rectus muscles were attached to the sclera with double armed sutures. Tenon's capsule and the conjunctiva were closed in two layers. For the secondary implantation technique the sclera covered ball was inserted into the intraconal fat, posterior to Tenon's capsule. Before implantation three double armed sutures were attached to the sclera at the 3, 6, and 9 o'clock positions. They were passed medially, laterally, and inferiorly through Tenon's capsule and the conjunctiva after insertion of the ball. The Allen implants,[4] with short tunnels through which the rectus muscles are drawn and sutured to each other, had all been inserted elsewhere.

The reasons for enucleation and the clinical characteristics in the four subgroups are summarised in Table 1. Patients who had sustained severe orbital trauma were excluded from this study.

The motility of the prosthesis and of the contralateral normal eye was measured with the Kestenbaum's limbus test.[5,6] The patients were provided with spectacles with frontoparallel acrylic glasses divided by a metric scale. For accurate motility readings pictures were taken of all patients wearing the Kestenbaum spectacles. During photography equal illumination by indirect lighting was achieved by placing the patient's head in a half globe with a white inner surface with two partly screened flash lights. The camera was placed on a stand in front (Fig 1). Pictures were taken with the patient looking straight forward and in three directions of gaze: abduction, adduction, and elevation (Fig 2). Depression was not measured because the upper eyelid covers the eye when looking downward. A water scale connected with the millimetre graduated glasses prevented false horizontal readings during photography. To enlarge the slides, they were projected on a screen to facilitate motility reading. Motility readings were performed with the temporal limbus as a landmark for adduction and the nasal limbus as a landmark for abduction. The inferior pupillary border was used as a landmark for measuring elevation. The position of these landmarks in the primary

*Table 1 Patient characteristics*

| | *Primary baseball implant (n=15)* | *Allen implant (n=12)* | *Secondary baseball implant (n=11)* | *No implant (n=11)* |
|---|---|---|---|---|
| Reason for enucleation: | | | | |
| Ocular trauma | 3 | 1 | 7 | 6 |
| Painful blind eye | 5 | 6 | 1 | 3 |
| Melanoma | 7 | 5 | 2 | 1 |
| Unknown tumour | – | – | 1 | 1 |
| Age at enucleation (years) | 47·9 (17–80) | 50·6 (37–65) | 22·8 (6–48) | 28·7 (7–63) |
| Age at implantation (years) | 47·9 (17–80) | 50·6 (37–65) | 40·3 (21–67) | – |
| Time interval between enucleation and investigation (years) | 1·9 | 2·2 | 19·4 | 18·9 |
| Prosthesis weight (g) | 1·9, SD 0·6 | 2·0, SD 0·6 | 1·5, SD 0·5 | 3·0, SD 1·1 |

position of gaze (when looking straight forward) was used as point of reference. In this way excursions of 0·5 mm or more could be determined. The mean motility in abduction, adduction, and elevation and the mean of the excursion in those three directions were calculated for each subgroup.

Values are expressed as mean with standard deviation (SD). Statistical analysis was performed by the two-tailed Mann-Whitney U test for comparisons of means between groups. To calculate the correlation coefficients the nonparametric one-tailed Spearman rank correlation test was used. For all analyses $p<0.05$ was considered statistically significant.

## Results

Table 2 shows the results of our measurements. The motility of the artificial eye was reduced substantially in all patients as compared with the motility of the contralateral eye. A motility loss of 50% or more was found. The mean motility in the primary baseball group averaged 2·3 mm, in the Allen implant group 2·2 mm, in the secondary baseball group 1·7 mm, and in the group without an implant 1·1 mm. The primary baseball and Allen implant patients had the best motility, whereas patients without an implant had the poorest motility. The motility of the artificial eye in the secondary implant group was intermediate. We found no correlation between the motility and the prosthesis weight nor between motility and the age of enucleation, the age at implantation, or the time interval between the date of enucleation and the date of investigation in each subgroup.

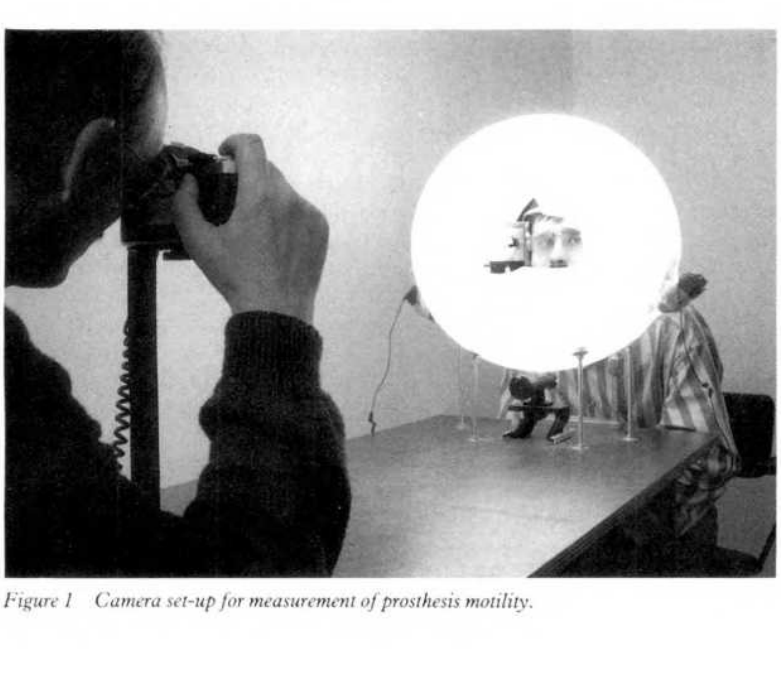

*Figure 1 Camera set-up for measurement of prosthesis motility.*

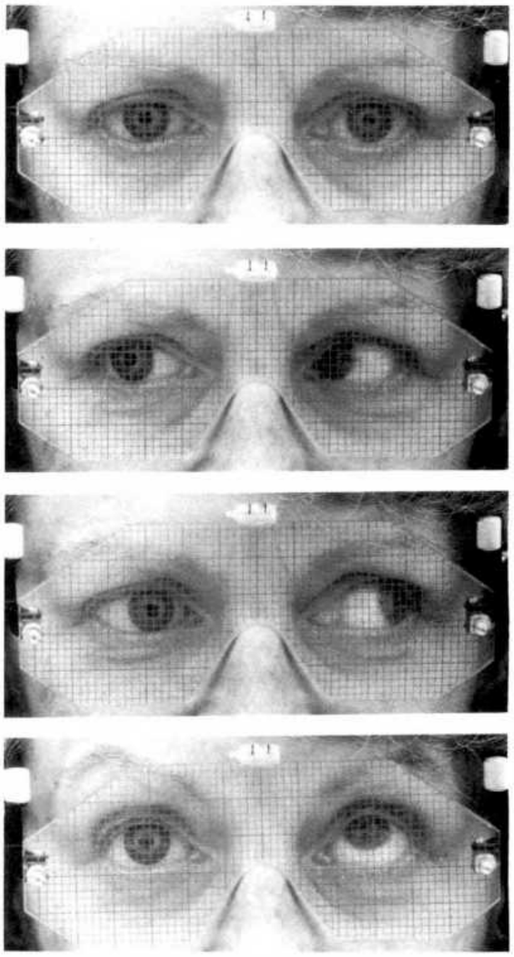

*Figure 2 Patient looking straight forward and in the three directions of gaze.*

## Discussion

A noticeable lag of movement of the prosthetic eye was measured in all four subgroups in the extreme directions of gaze. This loss of motion may be explained by orbital changes which follow enucleation, shortcomings in the current prothesis fitting techniques and/or surgical techniques, fibrosis of the extraocular muscles, and inadequate transmission of movement from the anterior surface of the socket to the posterior surface of the prosthesis. Other authors[6–8] also measured a poor overall motility of the prosthesis after enucleation.

The Allen implant, a buried quasi-integrated 'motility' implant,[9] has a flat anterior surface to which the flat posterior surface of the prosthesis is adapted. By this closer coherence the motility of the prosthesis is meant to be enhanced. Despite the design the Allen implant did not show better motility than the primary baseball implant. Apparently, as has been previously suggested,[7,10,11] the motility of the prosthesis, which rests in the conjunctival sack and is held in place by the lids, is derived from retraction of the fornices by contraction of the different rectus

*Table 2 · Prosthesis motility*

| | *Primary baseball implant (n=15)* | *Allen implant (n=12)* | *Secondary baseball implant (n=11)* | *No implant (n=11)* | *Contralateral, normal eye (n=49)* |
|---|---|---|---|---|---|
| Abduction (mm) | 2·2 (0·9) | 2·5 (1·1) | 1·6 (0·7) | 1·3 (0·6) | 8·6 (1·9) |
| Adduction (mm) | 2·1 (0·9) | 1·6 (0·9) | 1·6 (0·8) | 1·4 (0·9) | 8·0 (1·4) |
| Elevation (mm) | 2·7 (1·6) | 2·4 (1·3) | 2·0 (1·2) | 0·6 (0·7) | 5·5 (1·6) |
| Mean (mm) | 2·3 (0·8) | 2·2 (0·8) | 1·7 (0·6)* | 1·1 (0·5)† | 7·4 (2·1) |

*Significantly different from the values in the primary baseball implant group (U=43).
†Significantly different from the values in the primary baseball implant group (U=16·5), the Allen implant group (U=15), and the secondary baseball implant group (U=21).
Standard deviations in parentheses.

muscles with simultaneous relaxation of the opposing muscles, rather than from transmission of movement from the implant to the prosthesis. The Allen implants are prone to tilt in the orbit after implantation; the lower and temporal edges of the anterior surface of the implant mostly protrude, while the upper and nasal edges are tilted backwards. This may explain the difference in maximal excursion of the prosthesis in abduction and adduction in this subgroup (Table 2).

We did not find a relationship between the weight of the prosthesis and the motility in each of the four subgroups. Consequently, we could not confirm the concept[12] that the weight of the artifical eye has an effect on motion because it would take more energy and more friction to set a larger mass in motion. As was to be expected, the weight of the prosthesis in the group without an implant was higher than in the 'implant' subgroups. On average the weight of the prosthesis for the patients with a secondary implant was less than for the patients with other implants. This is explained from the finding in a previous study[13] that secondary implants generally are situated more anteriorly in the orbit than primary implants.

The implantation of a baseball implant after enucleation is a relatively new technique.[2] In our centre it was introduced in the early 1980s. From that time onwards (nearly) all patients routinely received a primary baseball implant following enucleation. Consequently, the primary implant group includes patients who were enucleated since the baseball implant was introduced, whereas in the secondary implant group the patients were enucleated before then. This explains the difference in time interval between date of enucleation and investigation in the two subgroups (Table 1).

The primary baseball and Allen implant group comprised relatively more patients who underwent enucleation for malignant melanoma, whereas in the secondary implant group and in the group without an implant relatively more patients were enucleated for ocular trauma. The differences in age at enucleation in the subgroups (Table 1) may be explained by the fact that malignant melanoma is usually seen in later life and ocular trauma in earlier life. The majority of patients who underwent enucleation for ocular trauma did not receive an implant immediately after the enucleation, probably for fear of extrusion.

The prosthesis motility associated with various implants could be compared by the method used. In contrast to De Voe,[10] who stated that a delayed implant does not improve the movement of the prosthesis, we found that the insertion of an implant, be it primary or secondary, markedly improves the motility. This phenomenon has also been noted by other authors.[6,12] Because we could not demonstrate a relationship between the weight of the prosthesis and motility, the better prosthesis motility in the implant patients cannot be explained by the decreased weight of the prosthesis required after insertion of an implant. We further concluded that there is no need to prefer an Allen implant to a primary baseball implant for motility reasons. On the other hand, the Allen implant suffers some disadvantages over spherical implants, such as uncomfortable socket, difficulty in prosthesis fitting, insufficient volume substitution, and tilting of the implant with exposure of the sharp edges and high risk of subsequent extrusion.[14,15] The baseball implant, on the contrary, usually corrects the orbital volume deficit adequately. In contrast to the Allen implant, which can be inserted only at the time of enucleation, the baseball implant can be used as a primary as well as a secondary implant. Furthermore the baseball implant permits additional volume substitution by insertion of a subperiosteal implant when a noticeable volume deficit is still apparent.

The numbers in Table 2 represent the motility in the extreme directions of gaze. In normal contact and in personal interactions, however, these extreme eye excursions are usually not applied. So the loss of motility on the affected side, which we found by measuring in these ranges, is not so dramatic in practice as the values might suggest. Often it was impossible to point out the affected side at first sight, especially in those patients with a primary baseball or an Allen implant, whereas during photography the enucleated side showed itself only when the patient was asked to look in the extreme directions of gaze. Apparently, as other authors[3,16,17] also noted, adequate motility in small excursions and good 'quick motion' in conversation are more important for preserving a natural appearance.

Better prosthesis motility in extreme eye excursions was linked with better motility in small excursions. So immediate prosthesis movement in small excursions concurrently with the fellow eye was found to be best in the primary baseball and Allen implant group, less in the secondary implant group, and the least in those patients without an implant.

From the foregoing it is clear that the primary baseball implant is preferred after enucleation. This implant restores the patient's physionomic aspect very well, in both a cosmetic and functional sense.

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# Postinflammatory cataracts in the mouse: induction by human mycoplasma-like organisms

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## Abstract

**Cataracts often occur in humans secondary to uveitis. Uveitis may be caused by various infectious agents, but rarely is the agent detected in the cataract. Mycoplasma-like organisms (MLO) were recently reported to cause human uveitis and retinitis. Cataracts were often present in those inflamed eyes. MLO are intracellular cell wall deficient pathogenic bacteria. They are pleomorphic tubulospherical and filamentous organisms with a characteristic ultrastructural appearance. No MLO culture system has been found despite 20 years of effort. The diagnosis of MLO disease rests on detection of the organisms in parasitised cells by a transmission electron microscope and response to antibiotics. In human intraocular inflammatory disease MLO are detectable in parasitised leucocytes and retinal pigment epithelial cells at the disease sites. Inoculation of MLO from a human source into mouse eyelids produced intraocular, chronic, progressive, inflammatory disease, with intraocular leucocytes parasitised by MLO in 15 of 100 mice versus 0 in 200 controls ($p<0·05$). This report describes the cataracts with MLO-parasitised intralenticular leucocytes in the inflamed eyes of 14 of those 15 mice versus 0 in 200 control mice ($p<0·05$). The results indicate that MLO penetrated the lens capsules to produce the cataracts, and they suggest that MLO could cause human cataracts. Alternative methods for detection of MLO and rifampin treatment of MLO intraocular disease are discussed.**

Cataracts often occur in humans as a result of intraocular chronic inflammatory disease, in both idiopathic intraocular inflammatory disease and inflammation caused by specific infectious agents.[1,2] The mechanism of postinflammatory cataract formation is complex and poorly understood, and only rarely is an intralenticular infectious agent found.[1,2] Mycoplasmas are cell wall deficient bacteria assigned to class Mollicutes.[3] Mollicutes ('mycoplasma') stain poorly with the usual biological stains and pass bacteria-retaining filters.[4] Mycoplasmas may be overlooked or confused with viruses.[4] They are pleomorphic tubulospherical and filamentous organisms with a characteristic ultrastructural appearance,[4] and they exist as extracellular and intracellular forms.[5] *Spiroplasma mirum*, an intracellular mollicute, produces inflammatory cataracts in young mice.[6] Other intracellular mycoplasmas are a well studied cause of chronic disease in plants.[7] Most plant intracellular mycoplasmas remain uncultivated despite over 20 years of effort.[7] Lacking a culture system, these forms are called 'mycoplasma-like organisms' or simply MLO.[7] Diagnosis of MLO disease rests on direct detection of these organisms in parasitised cells by transmission electron microscopy.[7]

MLO were recently reported to cause human uveal, retinal, and orbital chronic inflammatory disease with autoimmune features.[8–11] Cataracts were often present in these inflamed eyes.[8–11] In human MLO intraocular disease these pathogens have been reported in parasitised retinal pigment epithelial cells[12] and vitreous and/or aqueous leucocytes.[8–11] All leucocyte cell lines, including lymphocytes, monocytes, and polymorphonuclear leucocytes, may undergo MLO parasitisation.[8–16] Cells parasitised by MLO display distinctive fine structural alterations in cytoplasmic organelles and nuclei.[5,7–17] The nuclear alterations are probably the result of MLO nucleases[18] and expropriation of host cell nuclei acids by MLO.[16] Parasitisation by MLO results in host cell dysfunction, proliferation, and/or destruction.[7,8–17,19] MLO can be transmitted.[7] Inoculation of human ocular disease MLO into the eyelids of young mice produced intraocular inflammatory disease in 15 of 100 mice versus 0 of 200 controls after a three-month latent period.[20] MLO parasitised leucocytes were present in the intraocular inflammation.[14–16] Vasculitis was the initial lesion.[20] The disease was chronic and progressive.[20] Features of the progressive disease were extensive lymphocytic infiltrates, phthisis bulbi, exophthalmos, and cataracts.[20,21] This report provides details of those cataracts.

## Materials and methods

Four patients with intraocular chronic inflammatory disease served as sources of the MLO inocula. The clinical details are reported elsewhere.[22] The inflamed vitreous from each patient was removed by vitrectomy.[22] All specimens were available for laboratory studies by an approved protocol of the Investigational Review Board. No growth occurred from any of the vitreous specimens despite a large variety of culture techniques, and none of the specimens produced a cytopathogenic effect in various tissue culture cell lines.[22] Each specimen showed MLO parasitised leucocytes on transmission electron microscopy.[14–16] Each was stored at 4°C until animal inoculation.

*Table 1 Incidence of cataracts by mouse group*

| *MLO vitreous inoculated* | *Eye bank vitreous inoculated* | *Sterile saline inoculated* | *p* |
|---|---|---|---|
| 14/100 | 0/100 | 0/100 | <0·05 |

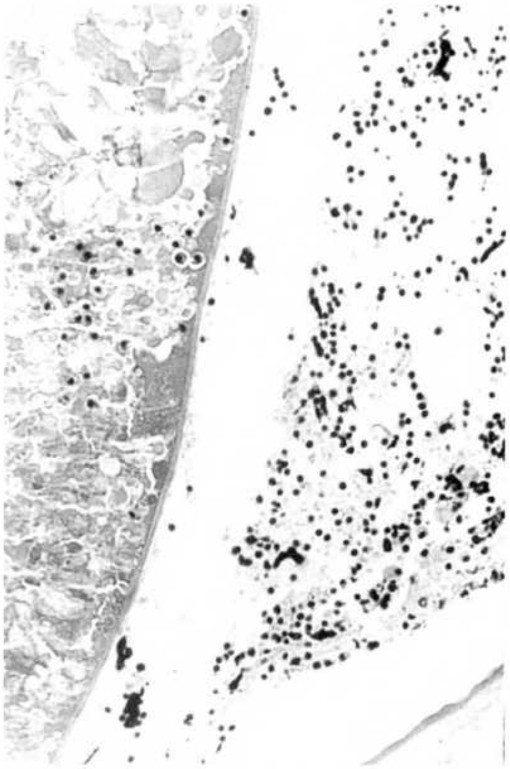

*Figure 1 MLO induced mouse cataract. Section through the anterior chamber and lens displays extensive intraocular chronic inflammation and severe cataractous degeneration. The identity of the intralenticular leucocytes is apparent on higher magnification. (H-E, ×240.)*

The animal investigation was conducted in accordance with an approved protocol of the Animal Care Committee. The animals consisted of 300 CD/1 male mice, 12–16 weeks old and weighing 15–20 g at the time of inoculation. Approximately 0·1 ml of MLO specimen from each of the four patients was inoculated into the lateral aspect of each lower eyelid of 25 mice for a total of 100 test mice. Vitreous from each of 10 eye bank eyes was inoculated into 10 mice for a total of 100 control mice. A further control consisted of sterile saline inoculated into the eyelids of 100 mice. This gave a grand total of 200 controls. All mice were observed twice daily five days a week for 12 months for visible persistent eye disease and spontaneous death. The results of those observations have been reported.[20 21] Three MLO inoculated mice with visible persistent ocular disease and three mice inoculated with eye bank vitreous were killed during observation months 4–7 by means of carbon dixoide in a closed container. Mice surviving at the end of 12 months were similarly killed.

The eyes and orbital tissue of all mice were exenterated, fixed in 10% formalin, and processed for routine haematoxylin-eosin stained tissue sections. Under a light microscope all eyes were examined for cataracts, and the incidence of cataracts by mouse was group calculated and compared. The relationship between cataracts and intraocular chronic inflammation was also determined. In addition portions of one lens from each of three MLO inoculated and three eye-bank inoculated mice killed during observation months 4–7 were finely minced, fixed in 4% glutaraldehyde, washed in 0·1 m cacodylate buffer, postfixed in osmium tetroxide, and embedded in Araldite. After polymerisation 1·0 μm thick sections were stained with toluidine blue and studied for cataracts under a light microscope. Sections displaying cataracts were ultrathin sectioned, stained with uranyl acetate-lead citrate, and studied for MLO parasitised intralenticular leucocytes.

## Results

### HISTOLOGICAL STUDIES

The incidence of cataracts by mouse group is shown in Table 1. The cataracts were bilateral in 11 mice and unilateral in three. All the cataracts were profound. They were peripheral in 19 lenses and diffuse in six. The cataracts were present only in eyes with intraocular inflammation and were associated with synechiae in 12 mice. The capsules appeared intact, but all 25 cataractous lenses showed varying numbers of intralenticular leucocytes (Fig 1). The leucocytes consisted primarily of lymphocytes, but a few monocytes, plasma cells, and polymorphonuclear leucocytes were also present.

### TRANSMISSION ELECTRON MICROSCOPIC STUDIES

The lenses of all three MLO vitreous inoculated mice displayed cataracts with intralenticular inflammation. MLO were readily detected in many of these leucocytes (Fig 2). The MLO parasitised leucocytes usually showed lysis of cytoplasmic organelles, irregular frayed nuclear contours, and chromatin lysis with clumping (Fig 2). None of the control lens sections displayed intralenticular leucocytes or MLO.

## Discussion

Nearly every mouse eye with intraocular inflammation had cataracts with intralenticular leucocytes, whereas none of the control eyes had cataracts or intralenticular leucocytes. MLO parasitisation of the intralenticular leucocytes was readily apparent by electron microscopy. The results indicate that MLO was the principal cause of the cataracts. Mollicutes contain various potent toxins.[18 19] The pathogenicity of MLOs in other tissues is grossly apparent and readily detectable by light and electron microscopy.[5 7–17 20 21 23] Tissue and cell lysis are characteristic features of MLO disease.[5 7–17 20 21 23] The smallest MLO particles measure 0·005–0·010 μm.[5 7–17] These particles are believed to be the ones that initiate cellular infection.[14–16] They penetrated the capsule with no apparent histological damage. Thereafter the larger MLO forms developed and persisted within the cataract. Ingress of leucocytes probably occurred through minute foci of capsular damage. The intralentricular inflammation was a response to both MLO and lens protein. Intralenticular leucocytes undoubtedly contributed further to the cataractous changes.

Postinflammatory cataracts often occur in patients with MLO intraocular disease.[8–12] Such cataracts are extracted and are available for

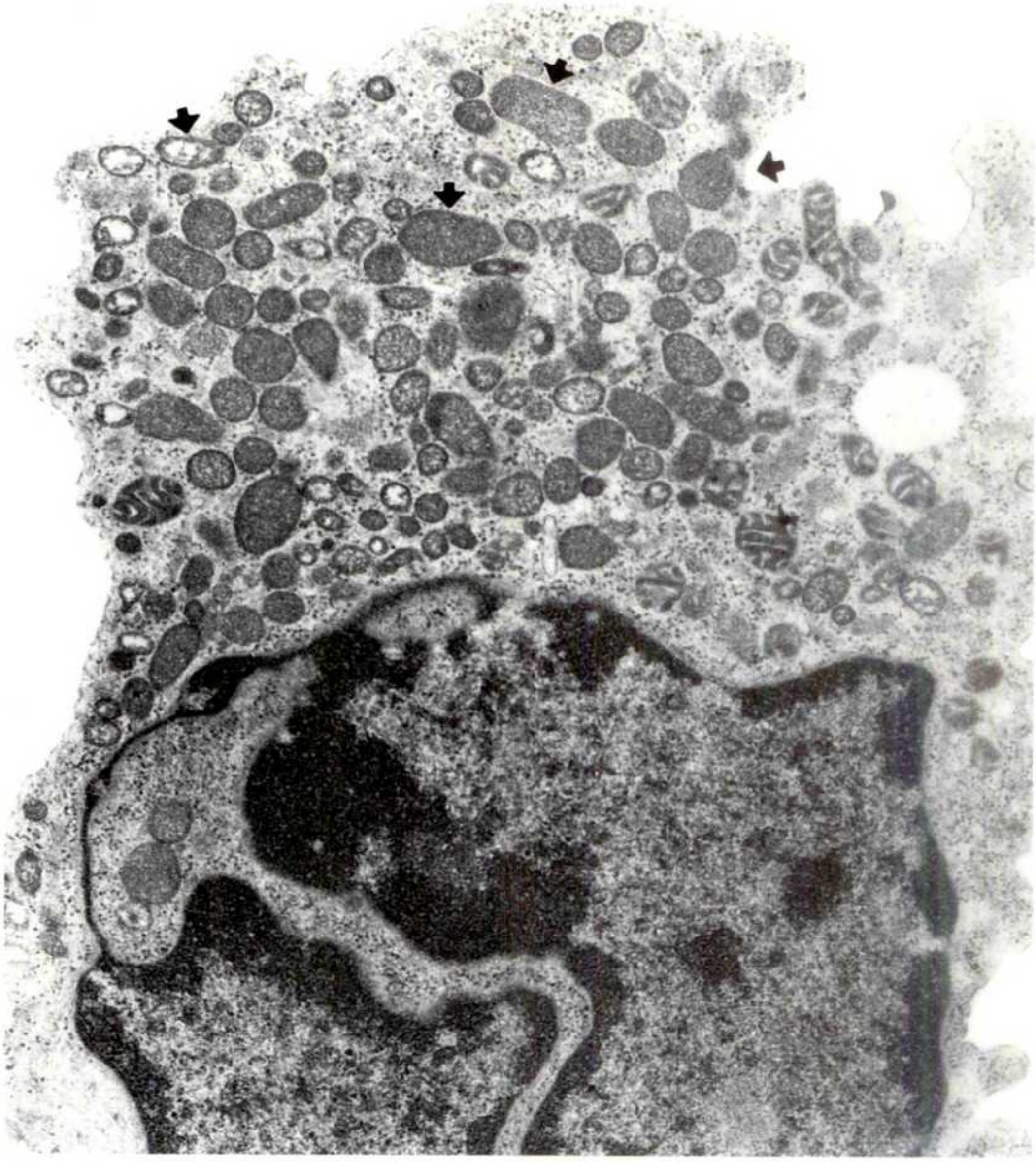

*Figure 2 MLO parasitised intralenticular leucocyte. Innumerable MLO fill the cytoplasm of an intralenticular monocyte from a cataractous lens (arrows). (Uranyl acetate-lead citrate stain, ×23 000.)*

laboratory study. From this investigation one would predict that MLO will be the pathogenic agent within these cataracts. It is noteworthy that intralenticular leucocytes are occasionally found in idiopathic postinflammatory cataracts.[2] The resemblence of these cataracts to MLO induced mouse cataracts is interesting.[2] MLO could explain the presence of the intralenticular leucocytes, and these could be readily studied for MLO.

Most human postinflammatory cataracts show no intralenticular inflammation.[1,2] MLO could also cause such cataracts. With minimal MLO intraocular inflammation and capsular damage leucocytes may not invade the lens. In this situation MLO alone could produce a cataract by parasitising and destroying lens tissues.[21,23] Detection of MLO by electron microscopy is difficult in the absence of leucocytes,[4,14-16] and other techniques could be valuable.[7,24] Prokaryotic cells often contain unique lipoidal substances not found in animal cells.[24] Sensitive assays for these substances are readily available.[24] The presence of such intralenticular substances would indicate a bacterial, possibly MLO, aetiology for the cataract. Detection of MLO in human cataracts would have diagnostic and therapeutic implications.

Rifampicin (rifampin) is beneficial in human and experimental animal disease caused by MLO.[8-12,25] It is a well tolerated antibiotic safe for long-term administration.[26] Its efficacy in MLO disease may be due partly to its active incorporation into leucocytes[27] and its possible inhibition of host cell nucleic acid expropriation by MLO.[16] Early rifampicin therapy would be expected to be beneficial in treating human MLO intraocular inflammation and the associated cataract.[28]

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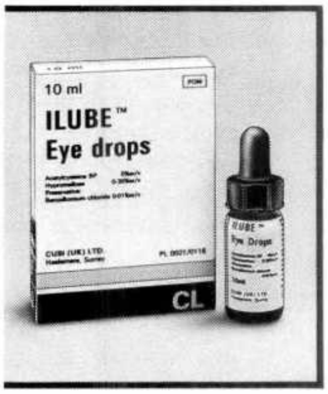

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# Ofloxacin compared with chloramphenicol in the management of external ocular infection

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## Abstract

**The safety and efficacy of 0·3% ofloxacin in treating bacterial ocular infections was compared with that of 0·5% chloramphenicol in a parallel-group, randomised clinical trial at five sites. Clinical and microbiological improvement rates were studied in 84 culture-positive patients. Patients with suspected bacterial ocular infections were evaluated for clinical improvement and were included in drug safety and comfort analyses. Clinical improvement did not differ significantly between drug treatments. All patients completing the study (79 assigned ofloxacin, and 74 chloramphenicol) showed clinical improvement. Clinical improvement in the culture-positive groups was 100% (41/41) after ofloxacin treatment, and 95% (41/43) after chloramphenicol treatment. Microbiological improvement rates were similar for the two drugs: 85% (33/39) improved with ofloxacin, and 88% (38/43) improved with chloramphenicol. Both drugs were well tolerated. Adverse reactions possibly due to the study medication occurred in 1% (1/89) of those who received ofloxacin, and in 4% (4/93) of those who received chloramphenicol.**

Bacterial infection of the outer eye is common, but there is a limited range of antimicrobial agents available for topical therapy. The search for new agents is influenced by the emergence of resistant bacterial strains to some topical preparations and by considerations of local and systemic toxicity.

In the following study the clinical efficacy of ofloxacin, a new antibiotic, was compared with that of chloramphenicol, an agent widely used against external bacterial ocular infections. This comparison was undertaken because chloramphenicol resistance has become established in several pathogens.[1 2] Moreover, rare but serious reactions have been associated with topical ocular use of chloramphenicol.[3-5]

Ofloxacin, a synthetic fluorinated quinolone first described in 1982, shows promise as an agent against external ocular infections.[6] Ofloxacin is exceptionally potent against a wide range of Gram-positive and Gram-negative bacteria and obligate anaerobes.[7 8] It is effective in vitro against many organisms that cause ocular infections (Table 1), for example *Haemophilus influenzae, Neisseria gonorrhoeae, Staphylococcus* species and *Streptococcus* species.[9 10] Ofloxacin also acts against *Pseudomonas aeruginosa*,[11] which is associated with ocular infections that are especially serious and difficult to treat.

Quinolones are bactericidal in mode of action; they specifically inhibit the bacterial DNA gyrase supercoiling function required by bacterial, but not eukaryotic cells.[12] In vivo, ofloxacin performs better than other fluoroquinolones with similar in vitro $MIC_{90}$ values (minimum concentration that inhibits 90% of isolates in vitro).[13] The pharmacokinetic indications[14 15] that it will be an effective topical ocular antibiotic have also been confirmed by clinical tests.[16] Chloramphenicol, isolated from *Streptomyces venezuelae* in 1947, has been an effective agent against external ocular infections for about 40 years.[17] Chloramphenicol acts by inhibiting prokaryotic protein synthesis.[18] The action of chloramphenicol is usually bacteriostatic, but it is bactericidal against *Haemophilus influenzae, Streptococcus pneumoniae*, and *Neisseria meningitidis*.[19]

*Table 1 The in-vitro effect of ofloxacin compared with other topical ophthalmic anti-infective agents against five major ocular pathogens, expressed as the $MIC_{90}$, the minimum inhibitory concentration against 90% of all bacterial strains tested.*[11]

| | *MIC (μg/ml)* | | | |
|---|---|---|---|---|
| *Organism (no)* | *Ofloxacin* | *Gentamicin* | *Tobramycin* | *Chloramphenicol* |
| *Haemophilus influenzae* (18) | 4 | 3 4 | 2 | 20 |
| *Pseudomonas aeruginosa* (68) | 4 | 8 | 4·4 | 128 |
| *Staphylococcus aureus* (79) | 0·5 | 1 | 2 | 16 |
| *Staphylococcus epidermidis* (68) | 0 5 | 32 | 64 | 32 |
| *Streptococcus pneumoniae* (21) | 2 | 7 | 16 | 4 |

## Patients and methods

This double-masked, parallel-group, clinical trial was conducted at five sites. Selected patients with suspected bacterial ocular infection were randomly assigned either 0·3% ofloxacin or 0·5% chloramphenicol ophthalmic solution for a seven-day treatment.

### PATIENTS

Patients were screened for several conditions. Other ocular disease, contact lens wear, and use of other ophthalmic medications or of systemic antibiotics were grounds for exclusion. Patients sensitive to chloramphenicol or to any quinolone were excluded. Those with uncontrolled systemic disease and pregnant or nursing women were not enrolled. Informed consent was obtained from all enrolled patients.

### SCHEDULE OF VISITS AND MEASUREMENTS

Symptoms were assessed by an ophthalmic examination (best corrected visual acuity, slit-lamp biomicroscopy, and ophthalmoscopy) at visit 1 (day 1), visit 2 (days 3–5), and visit 3 (day 8). On day 1 ocular cultures were obtained from

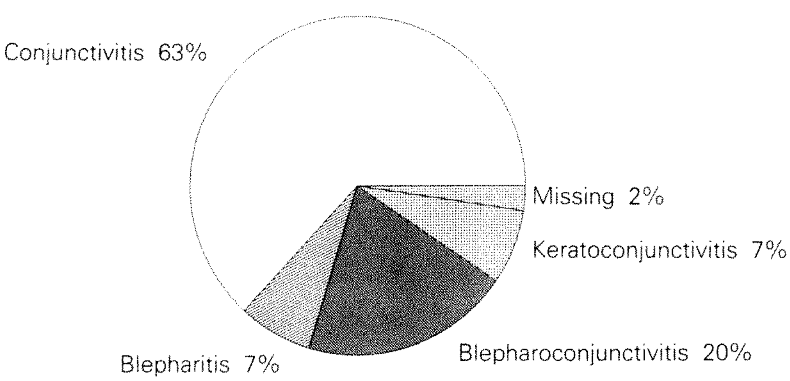

*Figure 1 Distribution of diagnoses in 84 patients who entered the study with positive ocular microbiological tests. (Sum does not equal 100% owing to rounding error.) *One case of blepharokeratoconjunctivitis included under keratoconjunctivitis.*

all patients as described below. Investigators applied the first drug dose, and patients were instructed to use their eye drops every 2–4 waking hours (according to severity as determined by the physician) on days 1 and 2 four times daily on days 3 through 7, and to stop treatment at least 12 hours before visit 3 on day 8.

Symptoms and drug tolerance were evaluated at visits 2 and 3. A second ocular culture was taken on visit 3 from patients whose first culture had given a positive result.

### MICROBIOLOGICAL METHODS

Ocular cultures were obtained by rolling the tip of a calcium alginate swab, moistened with sterile unpreserved saline, along the lid margin and conjunctival cul-de-sac of each affected eye. After the culture sample was obtained, each swab was placed in a sterile tube containing 1·0 ml of transport dissolving buffer solution (sodium citrate [dihydrate], sodium chloride, sodium acetate [trihydrate], potassium chloride, calcium chloride [dihydrate], magnesium chloride [hexahydrate], hydrochloric acid, sodium hydroxide, and purified water) and delivered to the microbiological laboratory within 4 hours for quantitative analysis.

On arrival at the laboratory the transport tube was vortexed until the swab fibres were finely dispersed. A sample of the suspension was directly plated on to a 5% horse blood agar plate (BAP) and a chocolate agar plate (CAP). A 1:10 dilution of the sample was prepared in sterile trypticase soy broth and also plated onto BAP and CAP. All sample plates were incubated for 48 hours at 37°C in 4% $CO_2$. Colony-forming units were counted, bacteria identified, and sensitivity tests to ofloxacin and chloramphenicol were performed.

### MICROBIOLOGICAL IMPROVEMENT

Classification of cultures as positive or negative followed the methods and classification of bacterial thresholds of Cable *et al.*[20][21] A culture was considered positive if the colony count exceeded the threshold for any bacterial class. For class A, the most virulent ocular pathogens (group A streptococci, other β-haemolytic streptococci, *S. pneumoniae*, all Gram-negative rods and *Neisseria* species), the threshold was above zero colony-forming units. For class B, α-haemolytic streptococci (other than *S. pneumoniae*), *Staphylococcus aureus*, micrococci, and *Branhamella catarrhalis*, the threshold was more than 10. For class C other *Staphylococcus* species (including *Staphylococcus epidermidis*) and *Bacillus* species, the threshold was more than 100. The threshold of class D, *Corynebacterium* species, was more than 10 000 colony-forming units.

Either eradication (zero colonies) or control of bacteria at visit 3 was scored as microbiological improvement. Bacteria were considered controlled if the colony count dropped below threshold values.

### CLINICAL IMPROVEMENT AND SAFETY

Clinical improvement was defined as a decline in symptoms of external ocular infection. The composite severity score (CSS) of 10 factors (lid erythema, oedema and crusting, palpebral and bulbar conjunctival hyperaemia, conjunctival oedema and discharge, corneal oedema, foreign body sensation, and pain) was determined for all patients. Biomicroscopy and symptoms were graded 0 for none, 1 for mild, 2 for moderate, and 3 for severe.

Drug comfort was determined from reported irritation or pain following use of the drug. Safety was assessed by reported adverse reactions and by comparing visual acuity, lens pathology and ophthalmoscopy before and after treatment.

### OVERALL IMPROVEMENT

Overall improvement, defined as showing both microbiological and clinical improvement at visit 3, was determined for initially culture-positive patients.

### STATISTICAL ANALYSES

Clinical, microbiological and overall improvement rates were compared by the Cochran-Mantel-Haenszel (CMH) test[22] stratified by the investigator. The CSS of the treatment groups was compared by a two-way analysis of variance. For all analyses a p value less than or equal to 0·05 was considered statistically significant.

## Results

A total of 167 patients with suspected bacterial eye infections were enrolled for clinical efficacy and safety evaluations. Age ranged from 19 to 81. On visit 1, 83 patients received ofloxacin, 84 received chloramphenicol. Treatment groups did not differ significantly in age, race, sex, iris colour, medical or ophthalmic history.

The frequencies of each diagnosis were the same in both treatment groups. Two conditions accounted for most cases. In the culture-positive group (Fig 1), conjunctivitis was diagnosed in 63% (53/84) of the patients, and blepharoconjunctivitis in another 20% (17/84). The remaining diagnoses were distributed among the following: blepharitis, blepharokeratoconjunctivitis, and keratoconjunctivitis. Two diagnoses were not recorded.

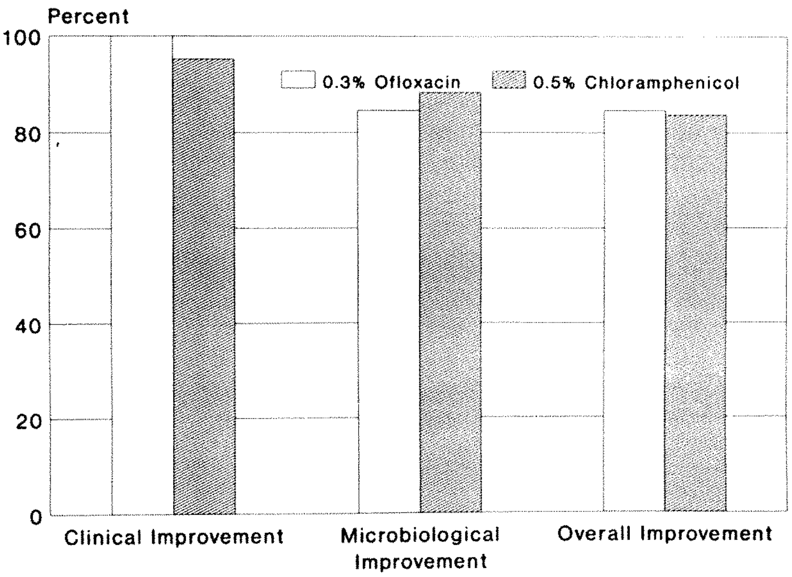

*Figure 2 Clinical, microbiological, and overall improvement rates for initially culture-positive patients treated for seven days with ofloxacin or chloramphenicol.*

MICROBIOLOGICAL ISOLATES

The culture-positive group comprised 84 patients who were microbiologically positive on day 1. Culture records were completed for 39 of 41 culture-positive patients assigned ofloxacin, and for all 43 patients assigned chloramphenicol.

Of 32 Gram-negative organisms isolated from ocular cultures on day 1 none was resistant to ofloxacin, but one was resistant to chloramphenicol. Of 152 Gram-positive organisms tested, one was resistant to ofloxacin, and four were resistant to chloramphenicol.

IMPROVEMENT IN CULTURE-POSITIVE GROUP

High improvement rates were obtained with both drugs. No statistically or clinically significant differences were found between treatments in microbiological, clinical, or overall improvement rates of the initial culture-positive group (Fig 2).

Microbiological improvement rates were 85% (33/39) for ofloxacin, and 88% (38/43) for chloramphenicol. Bacteria were eradicated by visit 3 in 79% (31/39) of patients given ofloxacin and in 77% (33/43) of those given chloramphenicol.

The two drugs were similarly effective against all bacterial genera and threshold classes encountered in this trial. For conjunctivitis due to common causative organisms the microbiological improvement rates are shown in Table 2.

Clinical improvement rates were 100% (41/41) for ofloxacin, and 95% (41/43) for chloramphenicol. Among patients with conjunctivitis clinical improvement rates were 100% (27/27) for ofloxacin treatment, and 96% (25/26) for chloramphenicol treatment.

*Table 2 The microbiological improvement rates of patients after treatment with ofloxacin and chloramphenicol against organisms commonly associated with conjunctivitis*

| | *Improvement rate* | | | |
|---|---|---|---|---|
| | *Ofloxacin* | | *Chloramphenicol* | |
| *Organism* | *% of patients* | *(No of patients)* | *% of patients* | *(No of patients)* |
| *Haemophilus influenzae* | 100 | 11/11 | 100 | 12/12 |
| *Staphylococcus aureus* | 96 | 26/27 | 87 | 20/23 |
| *Staphylococcus epidermidis* | 88 | 23/26 | 94 | 33/35 |
| *Streptococcus sp.* | 92 | 12/13 | 100 | 29/29 |

Overall improvement rates were 85% (33/39) and 84% (36/43) for ofloxacin and chloramphenicol, respectively. Overall improvement in culture-positive patients with conjunctivitis was 88% (22/25) for ofloxacin treatment and 85% (22/26) for chloramphenicol treatment.

In six of the 11 unimproved patients the bacteria present on day 8 were not present on day 1. Among those using chloramphenicol different species were present in 5% (2/43) (*Staphylococcus capitis; Staphylococcus epidermidis*) at visit 3. New organisms were present in 10% (4/39) of those using ofloxacin (*Micrococcus* sp., *Staphylococcus epidermidis*, α-haemolytic streptococci, and *Staphylococcus aureus*). In five unimproved patients the same bacteria increased above counts on day 1 in 13% (5/39) of patients treated with ofloxacin and in 9% (4/43) of those treated with chloramphenicol.

BIOMICROSCOPY, SYMPTOMS AND SAFETY – ALL PATIENTS

For all 167 patients there were no notable differences between treatment groups at day 1. CCS declined after treatment with both drugs, and no significant difference in any symptom was present at visit 3. No significant changes were detected by ophthalmoscopy during the study. No changes in visual acuity were correlated with any observed biomicroscopy changes.

There was no significant difference between groups in adverse reactions. Of 83 patients receiving ofloxacin, one reported a reaction described as haemorrhagic conjunctivitis and marked palpebral oedema which may have been drug induced. Four of 84 patients who received chloramphenicol left the study after various complaints (for example, atopic reaction; stinging and eye soreness; headache; lip ulceration) which were judged to be possibly due to the study medication. These five patients were discontinued from the clinical trial, and were not rechallenged with the study medication.

## Discussion

The development of novel anti-infective agents is required by the evolution of bacterial drug resistance because the effectiveness of any antibiotic can be impaired by resistant pathogens. The relative effectiveness and safety of alternative treatments must be considered in choosing any course of therapy, but a comparison of effectiveness and risk of side effects is especially important in evaluating the potential of a new therapeutic agent.

Chloramphenical is a potent, broad-spectrum antibiotic, and is still widely prescribed for external ocular infection. Unfortunately two factors threaten to erode its usefulness: the appearance of resistant bacterial pathogens, and the recognition of sometimes serious side effects associated with chloramphenicol therapy. The imminent need for alternative treatments notwithstanding, a prospective replacement must match the high performance of chloramphenicol while posing fewer risks.

Our study confirms that ofloxacin is a safe new antimicrobial agent effective in treating external ocular infection.[16] Ofloxacin performed as well as chloramphenicol in promoting microbiological, clinical, and overall improvement in patients with bacterial eye infections (Fig 2). Ofloxacin eradicated or controlled bacteria in 79% (31/39) of culture-positive patients compared with 76% (38/43) for chloramphenicol.

In vitro studies indicate that both ofloxacin and chloramphenicol are broad spectrum antibiotics.[23,24] However, the MIC$_{90}$ (minimum concentration that inhibits 90% of isolates in vitro) of ofloxacin is substantially lower than that of chloramphenicol for several important ocular pathogens. In fact, *P. aeruginosa*, a dangerous class A pathogen, is considered insensitive to chloramphenicol treatment.[25] The MIC$_{90}$ for ofloxacin is 4 μg/ml compared with 128 μg/ml for chloramphenicol against *P. aeruginosa*.[11] The MIC$_{90}$ was 0·5 μg/ml for ofloxacin against both *S. aureus* and *S. epidermidis*, whereas the respective values were 16 μg/ml and 32 μg/ml for chloramphenicol.[11]

Chloramphenicol resistance occurs in many pathogenic species, including *H. influenzae* and *S. pneumoniae*. High frequencies of resistance, ranging from 30% to 58% of clinical isolates, have been observed.[26–28] The potential for rapid spread of chloramphenicol resistance is high because plasmid-borne factors exist, and conjugative transfer of the plasmid occurs.[29–31] In contrast, ofloxacin-resistant strains seldom arise,[32] and the development of plasmid-borne resistance is viewed as unlikely.[33] Moreover, ofloxacin-resistant strains are typically slow growing and so unstable that they fail to compete with sensitive strains or revertants under ofloxacin-free conditions.[34] Though the 184 isolates sampled in this study did not differ significantly in their resistance to the drugs, five were insensitive to chloramphenicol, and one was insensitive to ofloxacin in vitro.

Along with efficacy safety is of primary importance in comparing drug treatment. Chloramphenicol can cause rare, but serious, blood dyscrasias, and fatal aplastic anaemia occurs in about 1 in 40 000 courses of systemic chloramphenicol therapy.[35,36] Topical ocular use of chloramphenicol has also resulted in blood dyscrasias and deaths from aplastic anaemia, an idiosyncratic reaction that is independent of dose.[3–5,37]

Adverse reactions to systemic ofloxacin occur at low rates of 2% to 7% of treated patients.[38] Clinical studies of 15 962 patients yielded about four adverse reactions per 100 patients who were administered an oral form of ofloxacin; such reactions were typically mild gastrointestinal complaints or minor nervous symptoms.[39] A low frequency, 0·5% (38/7566), of adverse reactions to an ophthalmic ofloxacin preparation was found in a post-marketing study completed in 1989 by Santen Corp., Japan (communicated to Allergan Inc.).

Ofloxacin possesses outstanding potency against a variety of pathogens, and is active against strains resistant to chloramphenicol and other antibiotics.[40–42] In comparing the utility of ofloxacin to that of chloramphenicol we must also consider the side effects of both drugs. Ofloxacin has negligible side effects when administered orally or topically. However, the risks associated with chloramphenicol have led some authors[43,44] to suggest using this antibiotic only when other agents fail. In considering effectiveness and safety, the clinical equivalence of ofloxacin compared with chloramphenicol has significance for the management of external bacterial ocular infections.

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CASE REPORTS

# Orbital xanthogranuloma in adults

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## Abstract

**The onset of periorbital xanthogranuloma in adults is rare and may be accompanied by haematological abnormalities and malignancy. The appearance of the eyelid lesions is virtually diagnostic, producing readily recognisable diffuse, yellow plaques, and affected patients should be investigated and reviewed regularly for systemic disease. Three cases are described, in which periorbital cutaneous plaques were associated with abnormal tissues in the superior part of the orbit; these abnormal tissues caused displacement or restricted movement of the globe or upper eyelid. The possibility that two cases represent a necrobiotic type of xanthogranuloma is presented. Nine years after the onset of xanthogranuloma one patient developed non-Hodgkin's lymphoma. A multiple-drug regimen of systemic chemotherapy, given for lymphoma, caused a marked clinical reduction in the periorbital xanthogranuloma.**

Periorbital xanthogranulomas arising in adults are rare and may be associated with the presence, or subsequent development, of a paraproteinaemia,[1-10] myeloma,[1,6,9] or leukaemia.[1,6] Local or systemic steroids, chemotherapy, radiotherapy, and plasmapheresis have been used to treat these lesions or any underlying haematological abnormality. The response to different modes of therapy are reported as being somewhat variable.

Intraorbital involvement in adult-onset xanthogranuloma has been reported in only a few cases. In this paper we present three cases of adult-onset xanthogranuloma, each with orbital involvement as shown by computed tomography (CT) (two cases) and at anterior orbitotomy. Two had features of necrobiotic xanthogranuloma.

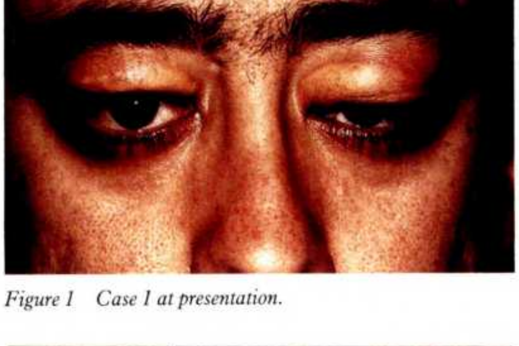


*Figure 1 Case 1 at presentation.*

## Case reports and histopathology

### CASE 1

A 22-year-old Greek male developed progressive, painless swelling of both upper eyelids. Biopsy showed idiopathic orbital inflammation. There was some subjective improvement with systemic steroid therapy, though this was discontinued because of the onset of grand mal epilepsy. A year earlier he had developed adult-onset asthma, for which he received inhaled salbutamol and weekly injections of Alavac-S (a desensitising vaccine). There was a past history of mild poliomyelitis at the age of 3 and petit mal at 7 years.

On referral to this hospital at the age of 24 the patient had normal vision and ocular motility. Prominent raised yellow plaques, involving the skin and underlying tissues of both upper eyelids, were present (Fig 1). The masses caused bilateral gravitational ptosis, though levator function was good. There was no relative proptosis, but both eyes were somewhat prominent (Hertel readings: 21 mm either eye). There was no regional

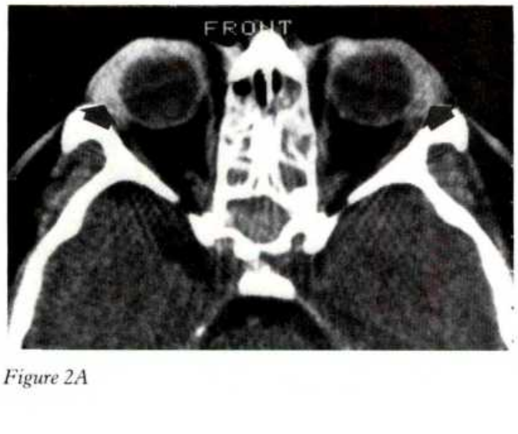


*Figure 2A*

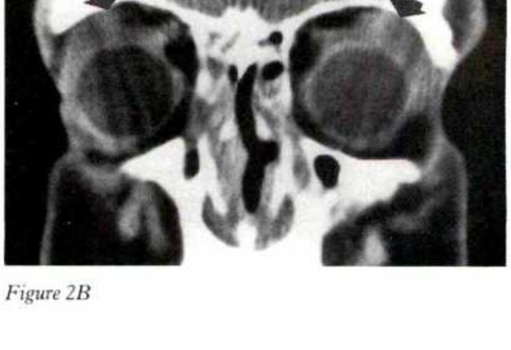


*Figure 2B*

*Figures 2A, B Case 1. Orbital computed tomography, showing soft-tissue masses anteriorly in the upper parts of the affected orbits (arrows).*

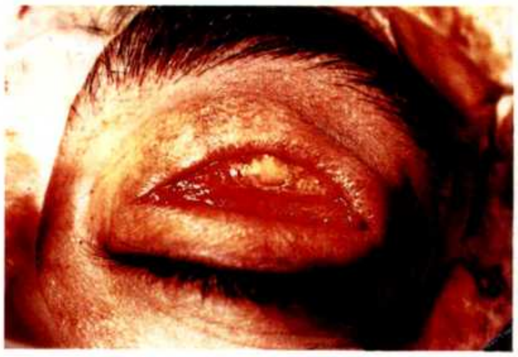


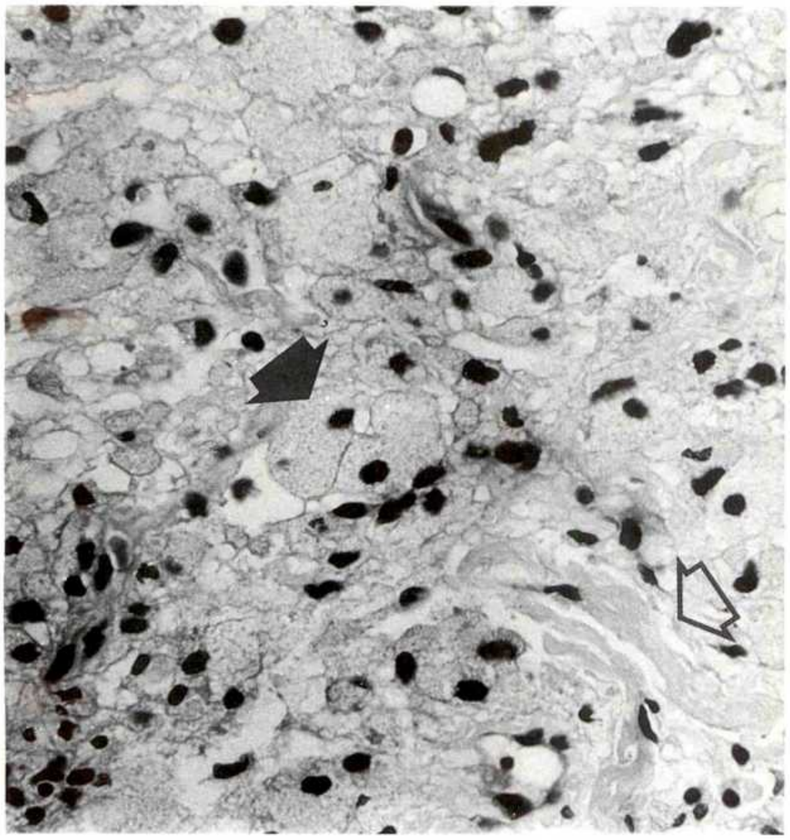
*Figure 3 Case 1. Intraoperative view of xanthogranuloma involving postseptal orbital tissues.*

lymphadenopathy, and systemic examination gave normal results.

Orbital CT scans showed a diffuse infiltration of the eyelids and the upper part of each orbit (Figs 2A, B). Chest radiographs showed slight enlargement of the left hilum, not typical of sarcoidosis.

There was a mild eosinophilia (0·56×10$^9$/l) and the erythrocyte sedimentation rate was 43 mm in the first hour (Westergren). With the exception of raised serum globulins (53 g/l; normal range 18–32), the levels of serum electrolytes, hepatic enzymes, and lipids were normal. Plasma protein electrophoresis showed a marked and polyclonal increase of gammaglobulins and a mildly raised $\alpha$-2 globulin concentration. Serum IgG concentration was raised (36·4 g/l), IgA slightly low (0·65 g/l), and IgM within normal range (0·62 g/l). Urinary protein concentrations were normal and no Bence-Jones proteins were detected. There were no detectable circulating autoantibodies, and serum concentration of the third component of complement was normal (C3=0·7 g/l). The fourth component was, however, slightly reduced (serum C4=80 mg/l), and C-reactive proteins were slightly increased (11·2 mg/l; normal range <10). The *Treponema pallidum* haemagglutination test (TPHA) and venereal disease research laboratory test (VDRL) were negative, and fasting serum triglycerides and cholesterol were within normal limits. The findings on bone marrow biopsy were normal.

*Figure 4 Case 1. Together with large numbers of cells with voluminous foamy cytoplasm (closed arrow) there are scattered inflammatory cells and foci of necrobiotic fibrous tissue (open arrow). (H-E, ×450.)*



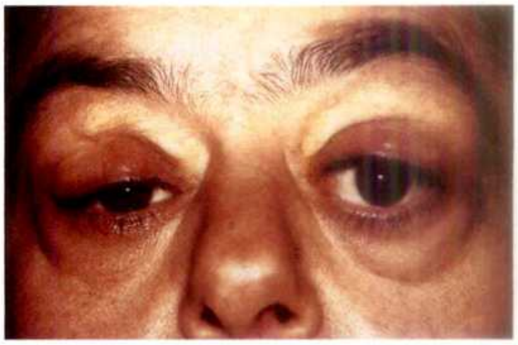


*Figure 5 Case 2 at presentation.*

At orbital biopsy an abnormal yellow material was present in eyelid skin, subcutaneous tissues, and orbicularis oculi, extending into the orbital fat and connective tissues (Fig 3). The fascia around the lacrimal glands was affected, but there was no involvement of the gland.

### PATHOLOGY

Histological examination of several biopsy specimens revealed extensive infiltration of eyelid dermis and anterior orbital tissues with histiocytes, many of which had voluminous, foamy cytoplasm (Fig 4). Scattered Touton giant cells were present, especially within the deep tissues, and there was patchy lymphocytic and plasma cell infiltration. The collagenous stroma showed foci of necrosis in the form of hyalinisation, fragmentation, and acellularity. Eosinophils were extremely rare and there were no neutrophils. Immunohistochemical staining reactions disclosed a polyclonal B-cell presence, with both $\varkappa$ and $\lambda$ light chains being demonstrable, while occasional IgM-forming cells complemented the predominantly IgG-related plasma cells.

### CASE 2

A 37-year-old Caucasian female developed diffuse swelling and yellow deposits within the skin and deeper tissues of both upper eyelids. At

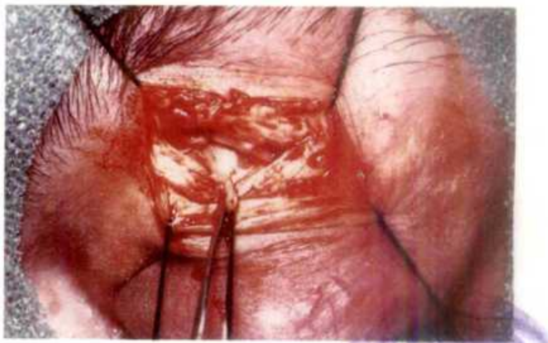


*Figure 6 Case 2. Intraoperative view of xanthogranuloma involving postseptal orbital tissues.*

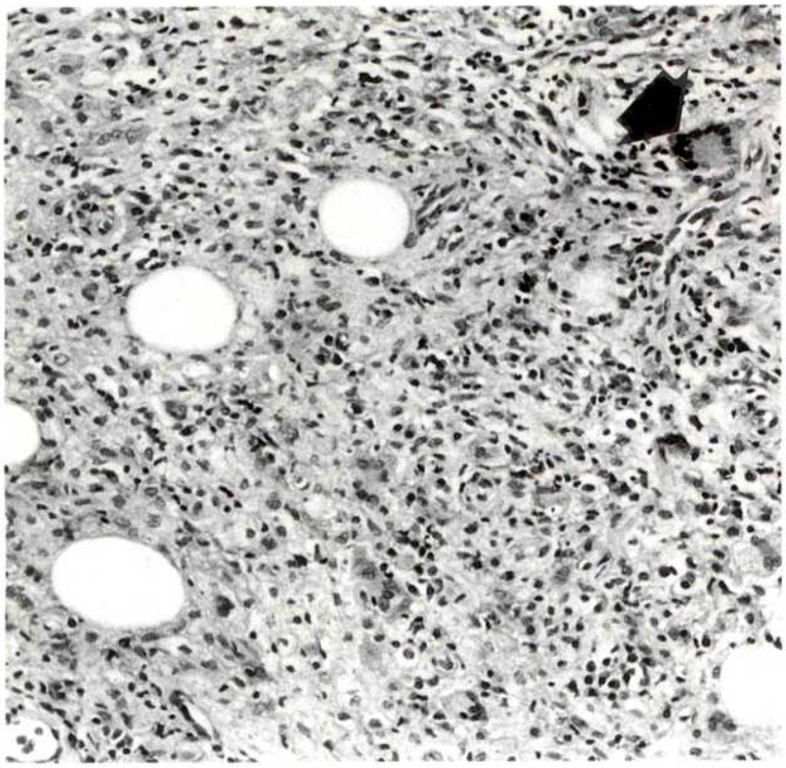


*Figure 7 Case 2. The orbital fat is infiltrated and largely replaced by histiocytes and scattered lymphocytes. Occasional giant cells are also present (arrow). (H-E, ×180.)*

the referring hospital the condition was thought to be 'pseudotumour' (idiopathic orbital inflammatory disease), and she was treated with systemic steroids, without improvement.

On referral, at age 43, she had yellow plaques extending widely over both upper eyelids. There was bilateral ptosis, greater on the right, levator palpebrae superioris function was moderate, and changes in skin creases of the upper lid were suggestive of bilateral disinsertion of the levator muscle aponeurosis (Fig 5).

Orbital biopsy revealed abnormal yellow material in the eyelid skin, in the orbicularis oculi muscles and in the orbital fat and connective tissues (Fig 6). The results of systemic investigation are not available for review.

### PATHOLOGY

Microscopy showed massive infiltration and replacement of orbital fat by histiocytes, with occasional foreign-body and Touton giant cell forms (Fig 7). Intercellular borders were frequently indistinct and many histiocytes had abundant foamy or vacuolated cytoplasm. There was a patchy lymphocytic infiltration, with occasional germinal centres, but plasma cells were sparse and eosinophils not observed. Stromal necrosis was not a conspicuous feature.

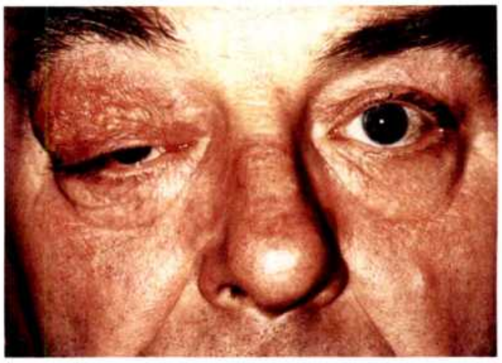


*Figure 8 Case 3. Extensive xanthogranuloma of right upper eyelid and orbit, causing 4 mm relative proptosis.*

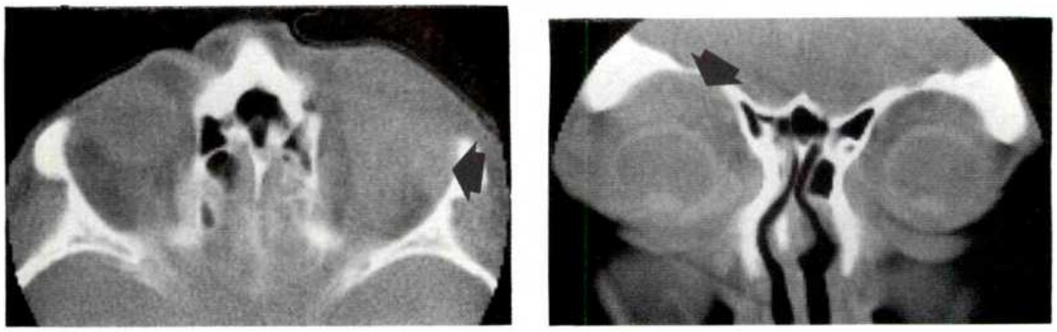
### CASE 3

The right upper lid of a 50-year-old Caucasian male developed a painless and slowly enlarging yellow lesion over a four-year period. This was thought to be a xanthelasma and was partially resected.

When first seen at this hospital at the age of 56 the right eye was displaced downwards by 2 mm, with 4 mm of relative proptosis. Supraduction and abduction of the right globe was slightly restricted. A large yellow plaque extended widely across the right upper lid, associated with poor function of the levator muscle, 7 mm of relative ptosis, and secondary brow elevation on the affected side (Fig 8). A mass was palpable, and visible through conjunctiva, in the superotemporal quadrant of the orbit. CT scans showed that it extended widely across the roof of the orbit (Figs 9A, B). Systemic examination, chest *x* ray, and serum electrolytes and lipids were all normal. The leucocyte count was $10\times10^9$/l, with a relative lymphocytopenia ($1\times10^9$/l) and eosinophilia ($1{\cdot}5\times10^9$/l).

At the age of 58, following transconjunctival biopsy, the patient underwent debulking of the lesion. Abnormal yellow tissue extended throughout upper lid skin, orbicularis oculi, and into the orbital fat and perilacrimal fascia.

Eighteen months later there was no progression of the eyelid lesion, but the patient developed extensive abdominal non-Hodgkin's lymphoma. The lymphoma was treated with multiple cycles of systemic cyclophosphamide, vincristine, doxorubicin (Adriamycin), prednisolone, and methotrexate. Following systemic



*Figures 9A, B Case 3. Orbital computed tomography, showing soft-tissue masses anteriorly in the upper parts of the affected orbit (arrows).*

*Figure 9A*

*Figure 9B*

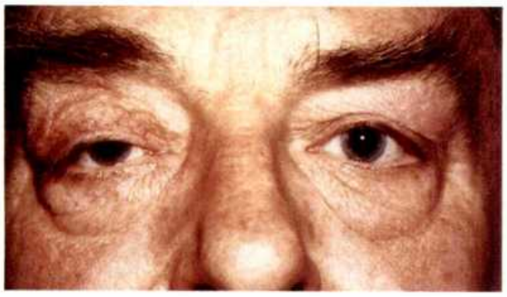


*Figure 10 Case 3. Resolution of proptosis and marked regression of eyelid lesion after systemic chemotherapy for abdominal non-Hodgkin's lymphoma.*

chemotherapy, there was a resolution of the proptosis and a marked reduction of the xanthogranuloma (Fig 10). A minor ptosis persisted and levator muscle function remained very poor.

PATHOLOGY

Histology of the excised tissue showed multiple foci of lymphocytic infiltration with occasional germinal centres. Plasma cells, together with considerable numbers of eosinophils, surrounded the centres of lymphoid activity, while the intervening stroma was largely replaced by histiocytes with generally voluminous, foamy cytoplasm (Fig 11). Touton giant cells were a conspicuous finding and there was moderate stromal necrosis (Fig 12).

## Discussion

Xanthogranulomas are granulomas in which the constituent histiocytes are filled with a lipid material. This material imparts a yellow coloration, both clinically for superficial lesions and on gross examination of resected specimens. Touton giant cells are also characteristic, these multinucleate cells having nuclei arranged in a 'wreath' round a nidus of eosinophilic cytoplasm and separated from the cell membrane by a rim of translucent, foamy cytoplasm.

Several histiocytic tumour-like lesions have been described, including the various forms of histiocytosis-X, generalised eruptive histiocytoma, reticulohistiocytoma, and some types of fibrous histiocytoma that may appear xanthomatous. Periocular xanthomatous lesions, with prominent Touton giant cells, form three categories – juvenile xanthogranuloma, necrobiotic xanthogranuloma, and Erdheim-Chester disease.

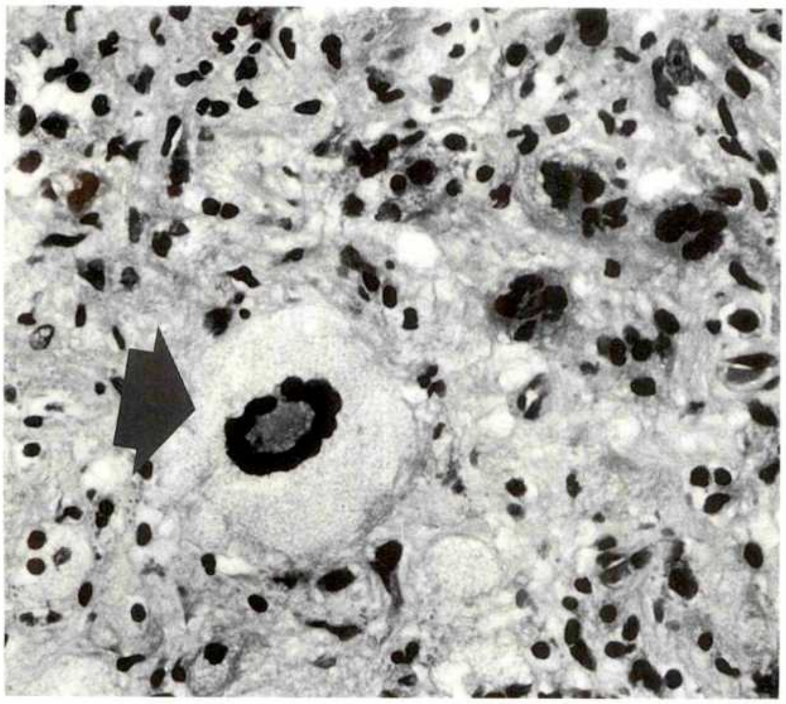


*Figure 11 Case 3. Orbital biopsy showed histiocyte infiltration with occasional chronic inflammatory cells and Touton giant cell (arrow). (H-E, ×450.)*

Juvenile xanthogranuloma presents as multiple skin or intraocular lesions and tends to resolve, either spontaneously or after systemic steroid treatment or radiotherapy.[11-13] Occasionally the lesions may occur in adults,[14] but orbital involvement, which is exceptionally rare, has been reported almost exclusively in children.[11 15]

Adult-onset xanthogranulomas may be associated with extensive systemic disease, involving particularly skeletal, renal, and hepatic tissues, being Erdheim-Chester disease or lipoid granulomatosis.[16] Periocular involvement is unusual with Erdheim-Chester disease, though cases with proptosis have been reported.[17-19]

In contrast, periorbital lesions, with a tendency to ulceration, are a predominant feature of necrobiotic xanthogranuloma.[1-10] These lesions display, between the areas of histiocytic accumulation and granuloma formation, a patchy hyaline necrobiosis with collagen destruction.[20]

Haematological abnormalities are common with necrobiotic xanthogranuloma and may include leucopenia, eosinophilia, a raised erythrocyte sedimentation rate, low serum complement, and occasionally a mild hyperlipidaemia.[1-10] Dysproteinaemia is almost universal, often with a monoclonal IgG paraprotein and occasionally with cryoglobulinaemia.[1 8] Indeed, Bullock and associates[7] suggest that serum immunoglobulins react with tissue lipids, these complexes being deposited in skin and eliciting a giant-cell foreign body reaction. Myeloma or chronic lymphatic leukaemia have also been reported in association with this condition.[1 6 9]

It is possible that the three cases reported here represent the necrobiotic type of xanthogranuloma, though the evidence is not conclusive. None had the systemic involvement or the widespread cutaneous lesions of Erdheim-Chester disease. Two patients (cases 1 and 3) had leucopenia or lymphocytopenia, eosinophilia, and a raised erythrocyte sedimentation rate. Case 1 also showed a polyclonal increase of serum immunoglobulin G, and, within the biopsies which displayed necrobiotic foci, there was a polyclonal lymphoid infiltration; $\kappa$ and $\lambda$ light chains, frequent IgG-forming plasma cells and occasional IgM-forming cells were identified. The third patient (case 3) had multiple areas of necrobiosis in the orbital biopsies and subsequently developed an intra-abdominal non-Hodgkin's lymphoma.

Reported treatment for necrobiotic xanthogranuloma includes local excision, radiotherapy, plasmapheresis, locally injected or systemic steroids, and the use of systemic or topical chemotherapy, such as chlorambucil, nitrogen mustard, cyclophosphamide, or melphalan.[1-10 21] The orbital xanthogranuloma in our case 3 resolved almost completely after potent multiple

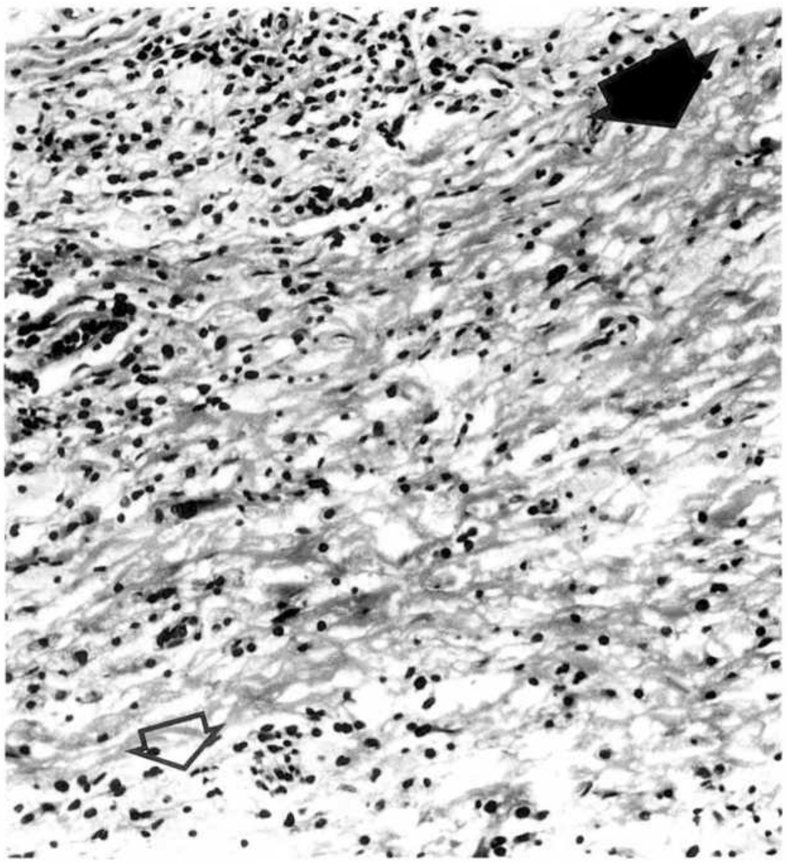


*Figure 12 Case 3. Foci of stromal necrosis are seen (closed arrow), along with diffuse lymphocytic infiltration and aggregates of foamy histiocytes (open arrow). (H-E, ×180.)*

drug chemotherapy (Figs 8, 10), this being in contrast to the rather variable response reported after other types of therapy.

It is imperative that the periorbital plaques of xanthogranuloma are recognised, because they may be part of a widespread systemic disease (Erdheim-Chester disease) or linked to a plasma cell dyscrasia or malignancy (necrobiotic xanthogranuloma). Unlike the thin lesions of periocular xanthelasma, periorbital xanthogranulomas are often thicker, larger, and may extend deeply into orbital tissues. Patients with xanthogranuloma should undergo systemic investigation, and, particularly where biopsy of the lesions shows hyaline necrobiosis, they should have continued clinical review for the development of plasma protein or other haematological abnormalities.

We thank the surgeons who referred the cases, and the staff of the Department of Medical Illustration, Moorfields Eye Hospital, for the clinical illustrations.

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# Choroidal vasculitis in acute posterior multifocal placoid pigment epitheliopathy

Richard F Spaide, Lawrence A Yannuzzi, Jason Slakter

## Abstract

**A 24-year-old Caucasian female presented with acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and associated infiltration round some of the larger choroidal blood vessels. This infiltration dissipated as the patient's clinical condition improved and did not induce any permanent alteration of the overlying retinal pigment epithelium. We suggest that the infiltration round the choroidal vessels was due to a choroidal vasculitis. The finding of choroidal inflammation in this case lends support to the hypothesis that choroidal vasculitis is an underlying pathological process in APMPPE.**

In 1968 Gass[1] described three young women who developed a rapid, but transient, loss of visual acuity associated with multiple yellow-white placoid lesions at the level of the retinal pigment epithelium (RPE). Although the presence of choroidal involvement could not be ruled out, the disorder was presumed to involve primarily the RPE and was named with the descriptive term, acute posterior multifocal placoid pigment epitheliopathy (APMPPE).[1] The concept that a choroidal vasculopathy played a part in the pathogenesis of APMPPE was the first made by Van Buskirk and associates.[2] Deutman and associates[3] suggested that an acute inflammation of the choriocapillaris might be the initial incident in APMPPE and the RPE changes were a subsequent manifestation. Several systemic findings associated with APMPPE involve a vasculitis – retinal vasculitis,[4-7] cerebral vasculitis,[8 9] and erythema nodosum[2 3 6] – which seems to support this hypothesis.

Direct evidence of choroidal vascular inflammation has remained elusive in APMPPE because the placoid lesions, as well as the melanin in the RPE and the melanocytes of the choroid, usually block visualisation of the choroidal vessels. We recently examined a young woman with APMPPE who had clinically discernible infiltrates of some of her peripheral choroidal vessels.

## Case report

A previously healthy 24-year-old fair-skinned, red-haired woman was referred for ophthalmological examination because of a four-day history of decreased vision in the right eye associated with severe headaches. She had a visual acuity of 20/60 in the right eye and 20/20 in the left. Fundus examination revealed multiple yellow-white placoid lesions at the level of the retinal pigment epithelium in both eyes (Figs 1A, B). The lesions were hypofluorescent in the early stages of the fluorescein angiogram but showed late staining. Two weeks after presentation the headaches stopped, but her visual acuity declined to counting fingers at 4 feet (120 cm) in the right eye and 20/400 in the left, secondary to bilateral foveal lesions. Fluorescein angiography at this time showed larger choroidal vessels in the subacute lesions (Fig 2), very slow filling of the choriocapillaris, and late staining of the lesions. There were no placoid lesions anterior to the mid-periphery.

In the periphery of both eyes some of the choroidal vessels were surrounded with patchy, segmental yellowish infiltration (Figs 3A, B and 4A, B). Several of the more prominently involved vessels clearly led to the ampulla of the vortex veins; in other involved choroidal vessels the classification of artery or vein could not be made.

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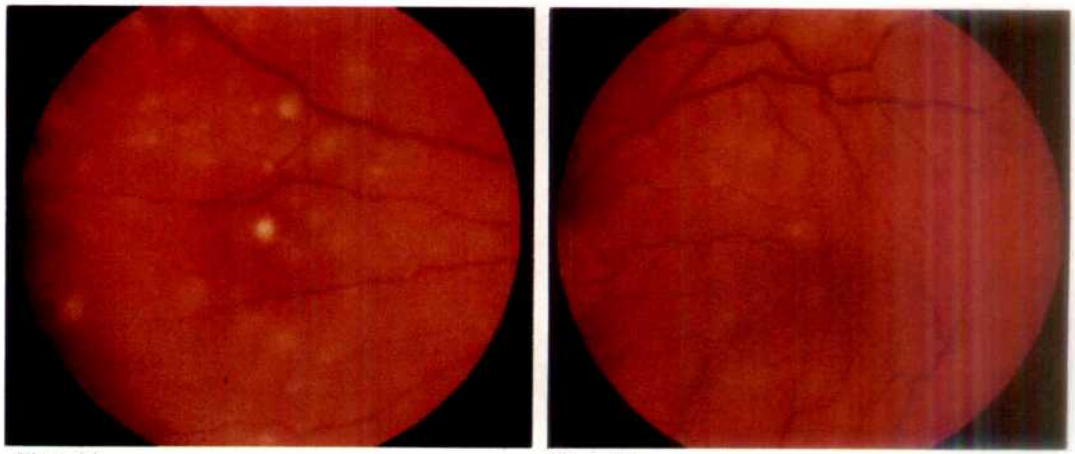

*Figure 1A* *Figure 1B*

*Figure 1 Fundus photographs of the patient with APMPPE on the day of presentation. A: Right eye. B: Left eye.*

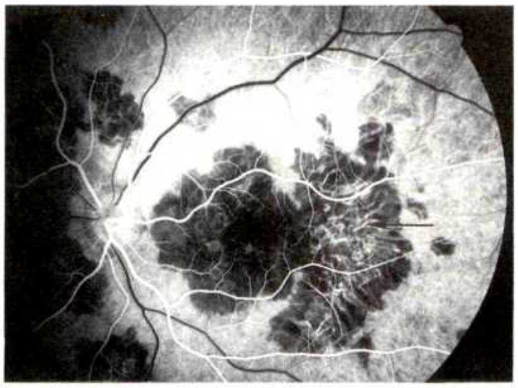

*Figure 2 Early phase fluorescein angiogram of subacute lesions in the same patient two weeks after presentation. The subacute lesions were characterised by resolution of the dense placoid lesions, atrophy of the involved retinal pigment epithelium, and unveiling of the choroidal circulation. In such lesions the larger vessels could be seen during the early stages of the fluorescein angiogram, but the blush due to the filling of the choriocapillaris was not present.*

The choroidal infiltration did not appear to involve the RPE by slit-lamp biomicroscopic examination with a three-mirror contact lens.

Over the next seven weeks both the placoid lesions and the peripheral choroidal vascular changes slowly resolved in parallel. Ten weeks after presentation the visual acuity was 20/40 in both eyes. The choroidal infiltrates had resolved in both eyes without detectable damage to the larger choroidal vessels or any discernible change of the overlying RPE.

During the course of her illness she was not noted to have any abnormalities of the external eye, anterior chamber, vitreous, or retinal vessels. Laboratory tests included a complete blood count with differential count, liver function tests, thyroid function tests, electrolytes, Lyme disease titres, and a chest roentgenogram. With the exception of a borderline low serum iron level, all tests gave normal results.

## Discussion

Infiltration round retinal vessels commonly occurs in conditions that cause a retinal vasculitis. We suggest that the infiltration round the choroidal vessels in our case of APMPPE represents a choroidal vasculitis or an accumulation of the by-products of inflammation round the involved choroidal vessels. A total of six patients are mentioned in four previous reports concerning retinal vasculitis associated with APMPPE,[4-7] and in each instance the involved vessels were veins. In our patient several of the involved choroidal vessels could be identified as veins, but no identification could be made about other vessels.

While choroidal inflammatory disease has been implicated in the pathogenesis of APMPPE, clinical signs of choroidal vasculitis in the acute stages of the disease have not been described. Several factors probably contributed to our visualisation of the choroidal infiltrates in the periphery, but not in the posterior pole. In the mid and far peripheral fundus the RPE is more attenuated and the larger choroidal vessels lie closer to the RPE than in the posterior pole.[10] The clinical focus of the disease, as implied by the name, is in the posterior pole, where the placoid lesions obscure the underlying choroidal vessels.

Many reported cases of APMPPE have had the prodromal symptoms of headache, fever, malaise, and myalgia.[11-19] These symptoms were ascribed by the patients or the investigators to a cold, influenza, or other viral infection. It has been presumed that these prodromal infections, directly or indirectly, caused an inflammation of the choroidal vessels, with APMPPE as a consequence. Although antecedent viral infections frequently have been implicated as the cause of APMPPE, the evidence for this supposition is far from compelling. In only one case of APMPPE was a virus, adenovirus type 5, isolated,[20] but this patient developed evidence of the viral infection 19 days after being affected by APMPPE, raising the suspicion that this association may have been coincidental. Another case of APMPPE associated with acute nephritis had a positive immunofixation test for the virus of epidemic nephritis,[21] but there was no increase in the antibody titre during the course of the disease.

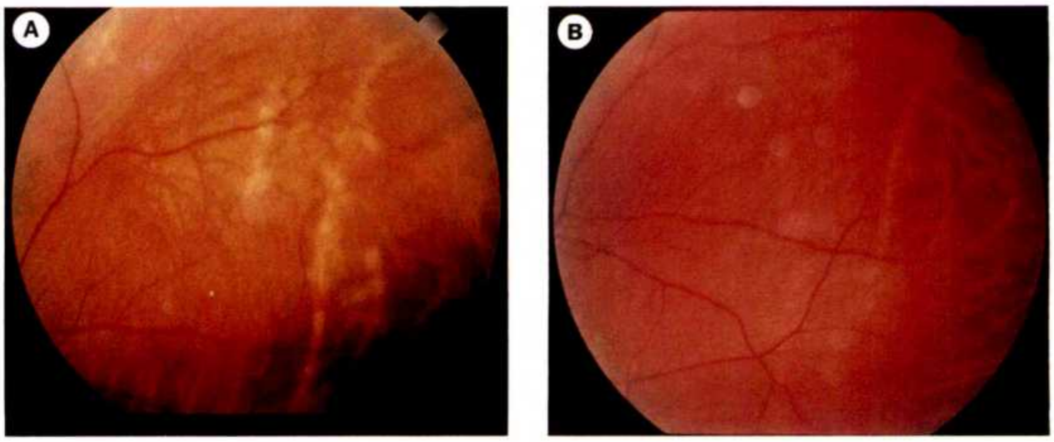

*Figure 3A* *Figure 3B*

*Figure 3 Choroidal inflammation in APMPPE. A: Infiltration round a choroidal vessel as seen three weeks after initial presentation. B: Disappearance of the choroidal inflammation 10 weeks after presentation, with no residual damage to the retinal pigment epithelium.*

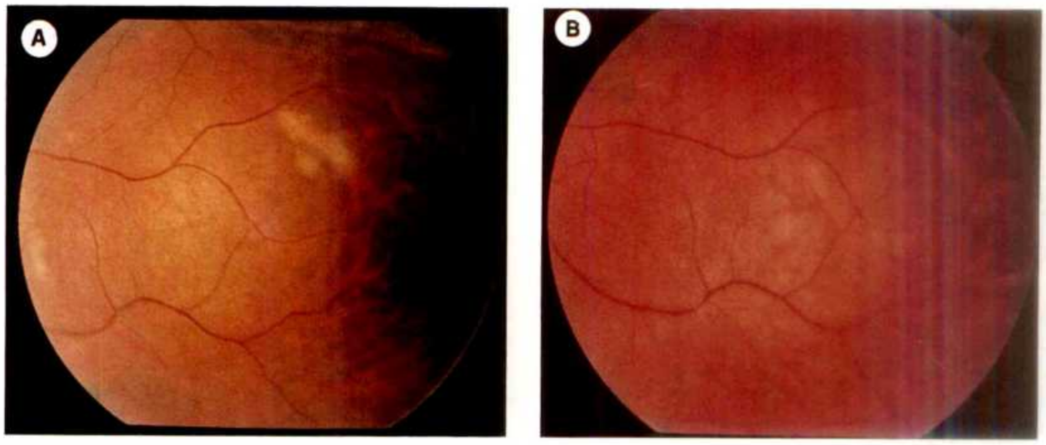

*Figure 4A*

*Figure 4B*

*Figure 4 Choroidal inflammation in APMPPE. A: A focal area of infiltration around a choroidal vessel as seen three weeks after presentation. B: Complete resolution 10 weeks after presentation with no damage to the pigment epithelium.*

While non-specific symptoms such as headache, fever, malaise, and myalgia can be associated with a cold or viral condition, they also can occur as part of a vasculitic syndrome.[22] It is possible that in some cases the headache, fever and malaise are manifestations of a transitory systemic vasculitis, of which APMPPE is a part. This vasculitis could account for the observation of cerebral vasculitis, retinal vasculitis, erythema nodosum, and in our case choroidal vasculitis in APMPPE. Although the finding of choroidal vascular infiltration in this patient does not prove that choroidal vasculitis is a requisite for APMPPE, it does lend support to the hypothesis that choroidal vasculitis plays a part in its pathogenesis.

The authors recently examined a second consecutive case of APMPPE after this report was written. While the disease was active scattered infiltrates around the choroidal vessels were found and these infiltrates appeared similar to those described in this report. The infiltrates resolved as the posterior pole lesions regressed. There was no abnormality of the overlying retinal pigment epithelium after the resolution of the infiltration.

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British Journal of Ophthalmology, 1991, 75, 688–689

# Choroidal involvement in lymphomatoid granulomatosis

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## Abstract

**A 13-year-old boy with evidence of pulmonary lymphomatoid granulomatosis developed monocular diplopia. Fluorescein angiography revealed bilateral choroidal involvement. Following treatment with vincristine, cyclophosphamide, and prednisone his diplopia resolved and the angiographic appearances returned to normal.**

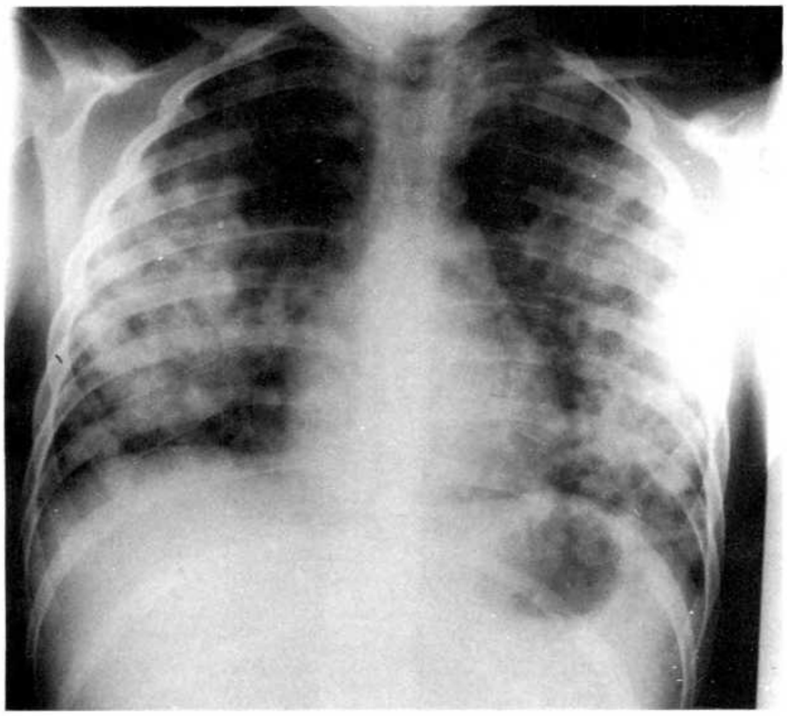

*Figure 1 Chest radiograph showing bilateral diffuse infiltrates.*

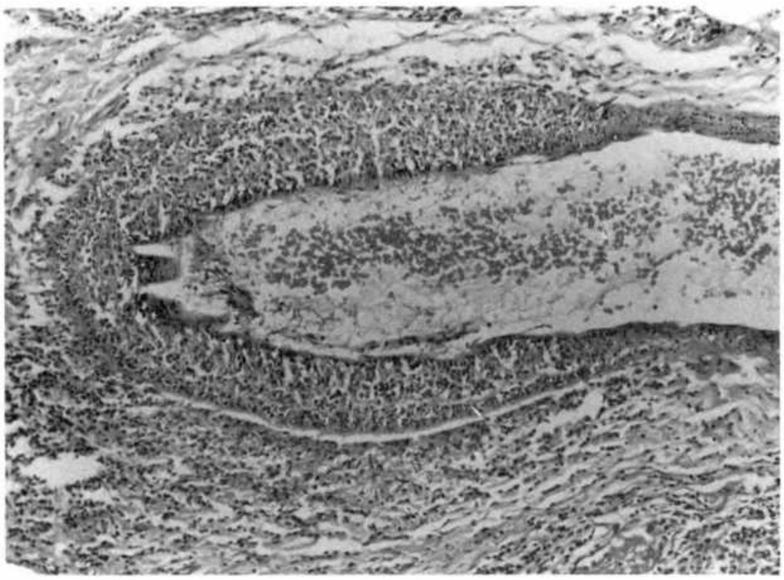

*Figure 2 Lung biopsy showing characteristic appearances of lymphomatoid granulomatosis. (H-E, ×135.)*

Lymphomatoid granulomatosis was first described by Leibow *et al* in 1972.[1] It is a form of angiitis with granulomatosis which predominantly affects the lungs, skin, nervous system, and kidneys. The condition is a multisystem disease with a mortality rate of up to 63%, death being due either to respiratory failure or to the development of malignant lymphoma. Characteristically the patient presents with widespread pulmonary infiltrates, dyspnoea, and respiratory failure. The central nervous system is involved in 40% of patients. Little, however, has been described of ophthalmic manifestations of the disease. It appears to be uncommon in Europe and unusual in children. The initial presentation of this boy has been previously reported.[2]

## Case report

At the age of 10, in 1981, this boy presented with a productive cough, fever, night sweats, and lethargy. Despite antibiotics he developed respiratory failure and cyanosis, dyspnoea, intercostal and subcostal recession, and crepitations in both lung fields. The liver and spleen were both palpable. A radiograph of his chest showed bilateral dense shadows (Fig 1). Other investigations gave normal results. Respiratory failure progressed, and he required mechanical ventilation. In view of this an open lung biopsy was performed. Macroscopically the lung was nodular, and histologically there were dense interstitial infiltrates of lymphocytes, polymorphs, and histiocytes (Fig 2).

These cells invaded the walls of many arteries with consequent obliteration, and there were many areas of necrosis and peripheral fibrosis. These are the features of lymphomatoid granulomatosis. He was treated with 60 mg of prednisone daily and made a very rapid recovery. However, withdrawal of steroids resulted in the return of his respiratory symptoms, and he was therefore kept on a small maintenance dose.

In May 1982 he developed bilateral parotid swellings and right facial palsy. A biopsy showed infiltration with lymphocytes and plasma cells, with a disordered arrangement of salivary gland ducts. Once again treatment with high dose prednisone resulted in a rapid resolution of these masses within 10 days. Concurrent skin infiltrates also disappeared. In November 1983 while on 10 mg of prednisone daily he developed monocular diplopia, and acute dizziness. A chest *x* ray at this time was normal as were the findings on general examination, apart from a raised blood pressure of 180/110 mm Hg. Investigation of his hypertension revealed that there was scarring of both kidneys on a dimercaptosuccinic acid scan and raised serum renin and aldosterone concentrations, although an intravenous pyelo-

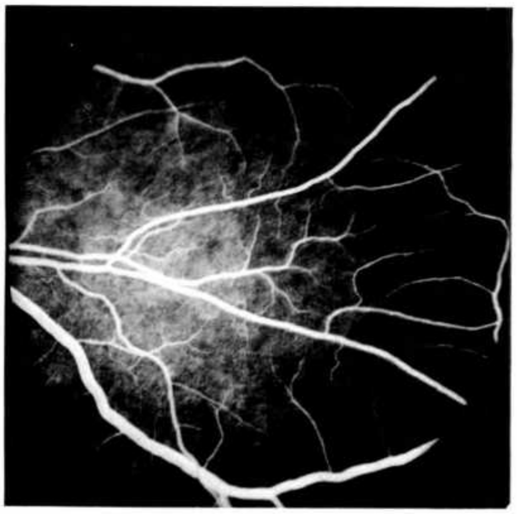

*Figure 3 Fluorescein angiogram showing hyperfluorescent choroidal lesion in the lower temporal quadrant of the left eye.*

gram and ultrasound picture were normal. This was thought to be consistent with previous involvement of his kidney with lymphomatoid granulomatosis.

Ophthalmic examination showed the cornea to be clear, and there was no evidence of lens opacities. Funduscopy showed an area of retinal oedema just below the macula. Fluorescein angiography showed a hyperfluorescent choroidal lesion just below and temporal to the macula of the left eye (Fig 3). The findings were consistent with a choroidal focus of lymphomatoid granulomatosis.

In view of the widespread nature of his disease he was started on vincristine, cyclophosphamide, and prednisone. Within two weeks his diplopia resolved, and a fluorescein angiogram performed one month later was entirely normal. Six years later he has had no recurrence of the ocular symptoms.

## Discussion

Lymphomatoid granulomatosis is a multisystem disorder characterised pathologically by a perivascular infiltrate of lymphocytes. Many organs may be affected but predominantly the lungs, central nervous system, and kidneys. This boy presented with monocular diplopia, and fluorescein angiography showed multiple choroidal involvement. Diplopia has been previously recorded in this condition secondary to lesions in the central nervous system and cranial nerves. Choroidoretinal involvement has been described in a 29-year-old male[3] and in two men aged 42 and 55 years.[4] Two of the patients previously reported had no ocular symptoms seven and 10 years after the onset, and the other had died with systemic involvement by the disease. Fauci *et al*[5] suggested that vincristine, cyclophosphamide, and prednisone were beneficial in this disease and caused more improvement than steroids alone. The boy described here responded dramatically to treatment with this combination, and his infiltrates disappeared.

Fluorescein angiography displayed the infiltrates in his choroid at a stage when routine funduscopy showed only retinal oedema.

This case again demonstrates that the choroid is yet another organ which can be involved with lymphomatoid granulomatosis. Fluorescein angiography aids its diagnosis, and treatment with vincristine, cyclophosphamide, and prednisone produced a dramatic and long lasting response in this child.

We are grateful to the North of England Children's Cancer Research Fund for support of Dr A D J Pearson.

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# Inadvertent application of silicone foam elastomer catalyst to the eye

N J Cook

**Abstract**

**Silicone foam elastomer is used extensively to treat granulating wounds. A case is presented in which the catalyst to the polymer was inadvertently applied to the eye. This produced conjunctival and corneal injury, which was slow to heal and resistant to conventional treatment. This form of injury has not previously been described.**

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A silicone foam sponge was being prepared by a nurse for pouring into the wound cavity of a pilonidal sinus by mixing 1 ml of the clear viscous catalyst (stannous di-2-ethylhexoate) with 10 ml of silicone. The nurse inadvertently touched the catalyst and brought it into contact with her right eye. The eye was immediately irrigated with water on the ward, followed by further irrigation with 500 ml normal saline in the Eye Casualty Department.

Visual acuity was 6/9 unaided (6/5 with $-1{\cdot}0$ dioptre sphere) right, and 6/6 unaided left. No injury to the lids was sustained. Mild inferior tarsal and bulbar conjunctival injection was noted, without fluoroscein staining or conjunctival shutdown. The cornea appeared normal, and there was no anterior chamber activity. Chloramphenicol ointment was prescribed.

The following day the right eye remained very irritable, with tearing and photophobia. The inferior tarsal and bulbar conjunctival injection was now marked, and there was an associated inferonasal superficial punctate keratopathy. Topical betamethasone four hourly was added to treatment.

One week later the inferonasal bulbar conjunctiva was still markedly injected and had become very chemotic. The epitheliopathy remained unchanged. Firm double padding, after instillation of betamethasone ointment and homatropine 2%, was carried out for three days. No objective or subjective improvement was noted.

Three weeks after injury the conjunctival injection had diminished, but the corneal epitheliopathy persisted, and the patient still complained of symptoms. Topical chloramphenicol and betamethasone were discontinued, and topical lubricants were prescribed twice daily.

After three months the superficial punctate keratopathy had only marginally improved, though the conjunctiva had fully recovered. Figure 1 shows the corneal appearance at three months, illuminated with a 495 nm fluorescein excitor filter. The epitheliopathy did not entirely resolve until six months after the initial injury. The corneal epithelium and stroma were normal, though the patient was still complaining of photophobia.

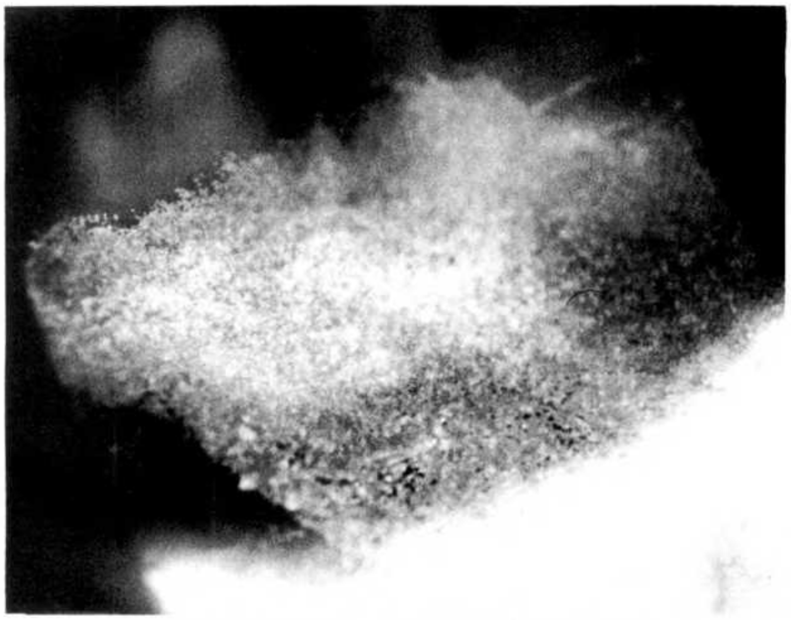

*Figure 1 Superficial punctate keratopathy at three months, demonstrated by fluorescein staining.*

## Discussion

Silastic foam sponges were first described for use in dressing pilonidal sinuses to 1975.[1] Since then their use in wound dressing has expanded to encompass abdominal, perianal, and perineal wounds, bed sores, and epispadias.[2] Warnings accompanying this product advise against prolonged contact with the skin, mouth, or eyes and suggest irrigation with water should they come into contact with the substance.

The catalyst, stannous di-2-ethlyhexoate, is an extremely water-insoluble ($<0{\cdot}10\%$ w/w, 10°C) thick viscous substance. It sticks to biological material and is not easily removed by water. This case highlights the difficulty in removing water insoluble substances from the ocular surface. A more suitable solvent, known to be innocuous to the ocular surface, such as liquid paraffin or polyvinyl alcohol, might be applied to the tip of a cotton bud and used to clear such ocular contaminants.

In view of the widespread use of this product and the potential hazard of its coming into contact with the eye, it is suggested that great care is required in its use and that irrigation with water of the affected area is insufficient as a first aid measure.

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*British Journal of Ophthalmology*, 1991, 75, 691–692

# Cleft anterior segment with maternal hypervitaminosis A

K Evans, M U Hickey-Dwyer

## Abstract

**We report a case of an 'hourglass' cornea and iris with reduplicated lens in the left eye of an infant girl. An excess of vitamin A products had been taken by the mother during pregnancy. Mechanisms by which vitamin A excess could have caused this are discussed.**

Vitamin A and its analogues have become readily available on the market. High doses have been used to treat deficiency states, acne, other dermatoses and also in combination with other vitamins in 'healthy diet' regimens.[1] In recent years many reports have appeared of birth defects in the children of users.[2] The present report is of an unusual congenital abnormality thought to be due to excess intake by the mother of vitamin A from a number of sources.

## Case report

A Caucasian girl born to a healthy 26-year-old mother and an unrelated 32-year-old father came to the Ophthalmology Department with a history of an 'enlarged left eye' since birth. Examination under general anaesthesia revealed a cornea and iris with an hour-glass shape as if partially cleaved in two. At the hour-glass junction peripheral anterior synechiae were found. The cornea measured 14·5 mm horizontally, a maximum of 10·5 mm veritcally (Fig 1). Intraocular pressure was normal. Double or reduplicated clear lenses were seen behind the iris lying in a horizontal plane. No fundal abnormality was found. The right eye appeared normal. General physical examination showed no abnormalities or dysmorphic features. Laboratory investigations including a full blood count; tests for blood urea and electrolytes and random glucose gave normal results. Tests for syphilis, *Toxocara* and viral serology for cytomegalovirus, herpes, and rubella gave negative findings. The peripheral blood karyotype was a normal 46 XX. Computed tomography of the brain and orbits showed the abnormal cornea and double lens but no intracranial abnormality (Fig 2).

There was no family history of eye disorders. A full history from the mother disclosed no past medical problems. During pregnancy cervical carcinoma in situ was diagnosed, which was not treated until after delivery of the infant. The pregnancy was otherwise uneventful. There were no symptoms during pregnancy suggestive of hypervitaminosis A. She had taken on average 10 capsules of royal jelly and six multivitamin tablets per week throughout the pregnancy. In addition she had consumed on average three meals containing liver per week during the first trimester only, which she had been informed would be beneficial.

## Discussion

Reduplication of the lens is very rare.[3,4] Hourglass cornea and iris with reduplicated lens giving the appearance of a cleft splitting the anterior segment into two halves has not previously been reported. Apart from unusual features of the diet, extensive investigation failed to find a possible cause. Royal jelly contains proteins, water, carbohydrates, trace elements, and vitamins B, C, and E. So far there have been no reports of congenital eye anomalies associated with maternal ingestion of royal jelly, or with

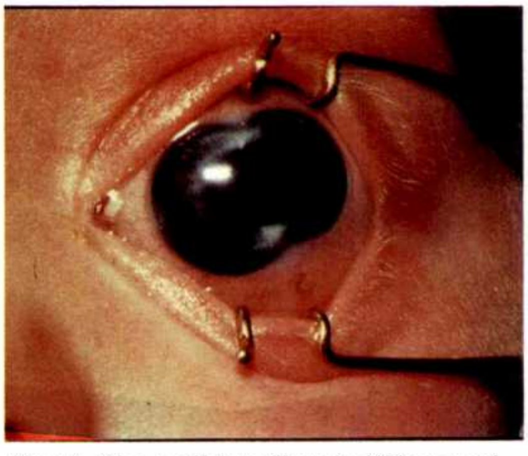

*Figure 1 Close-up of left eye, illustrating bifid cornea and iris.*

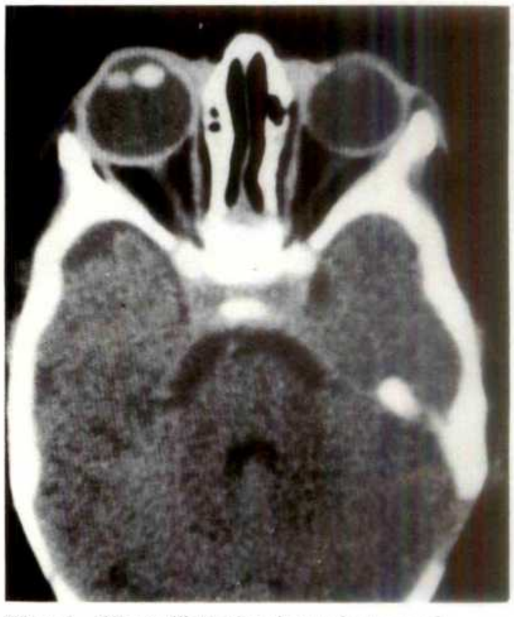

*Figure 2 CT scan illustrating abnormal cornea and reduplicated lenses.*

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cervical carcinoma in situ. Vitamin A, however, has been linked to many different teratogenic effects abroad, but not in Great Britain.[5]

Recent DHSS advice suggests that the dietary intake of vitamin A in pregnancy should not exceed 10 000 IU daily; teratogenic effects have been reported at doses as low as 20 000 IU per day. Proprietary multivitamin tablets may contain 7500 IU each. A significant source of vitamin A in food is liver. A normal 100 g portion may contain 12–20 times the recommended daily dose. A normal diet (without liver or supplements) will contain about 2500 IU.[6] We estimated that this mother took on average a daily dose of 25 000 IU in the first trimester.

Consent for blood vitamin A levels was not given, but the mother gave a clear history. Moreover, the history of vitamin and liver supplements was not asked about directly but volunteered when she was asked if she had an unusual diet during pregnancy. Therefore there is good circumstantial evidence that the fetus was exposed to high levels of vitamin A during the first trimester and that this was the cause of the resultant anomalies.

Affected infants have one or more features of a so called 'retinoid syndrome': ear defects, cleft lip and palate, craniofacial dysmorphism, cardio-aortic defects, thymic hypoplasia, hydrocephaly, and spina bifida. Ocular features include microphthalmia, anophthalmia, Goldenhar's syndrome,[5] and retinal and optic nerve anomalies.[1]

Past cases of lens reduplication have been associated with facial anomalies and syphilis.[3] It was assumed in at least one case that abnormal corneal tissue had interfered with lens vesicle migration from the surface ectoderm, splitting it in two.[4] It is known that excess vitamin A interferes with neural crest development.[5] Possibly in this case abnormal corneal development (known to involve neural crest cells[7]) interfered in a similar way with lens vesicle migration and development.

We are grateful to Mr D B Clements and Mr D Leighton for permission to report on their patient.

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# Acquired pigmentation simulating Peutz-Jeghers syndrome: initial manifestation of diffuse uveal melanocytic proliferation

J Donald M Gass, Ronald J Glatzer

**Abstract**

**A 74-year-old man with an occult carcinoma of the colon developed pigmentation of the mouth and penis typical of the Peutz-Jeghers syndrome as the first manifestation of bilateral diffuse uveal melanocytic proliferation. The simultaneous appearance of extraocular pigmented lesion and those in the uveal tract of both eyes of this patient provides further evidence that bilateral diffuse uveal melanocytic proliferation may be caused by activation of occult melanocytic naevus cells in response to either a hormone-producing carcinoma or to some other common oncogenic stimulus.**

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a paraneoplastic disorder causing visual loss in both eyes of patients with systemic, often occult carcinomas.[1-4] It is characterised by the development of (1) multiple subtle round and oval subretinal red patches that angiographically show a striking pattern of early hyperfluorescence; (2) multiple, slightly elevated, pigmented and non-pigmented, uveal melanocytic tumours, as well as evidence of diffuse thickening of the uveal tract; (3) exudative retinal detachment; and (4) rapid development of cataracts. The uveal melanocytic infiltration is composed of predominantly benign naevus cells. Metastasis of the uveal tumour has not been reported. Death caused by metastatic carcinoma usually occurs within 12 to 24 months. The cause of the ocular changes is unknown, and treatment is ineffective.

This report concerns a patient whose first sign of the BDUMP syndrome was the development of hyperpigmented patches on the mucous membranes of the mouth and penis in a pattern typical for the Peutz-Jeghers syndrome. It is the first report of simultaneous development of non-ocular pigmentation in a patient with BDUMP.

## Case report

In April 1988 an apparently healthy 74-year-old man developed hyperpigmented macules on his lips and penis. A dermatologist made a diagnosis of Peutz-Jeghers syndrome and recommended examination to exclude intestinal polyps. A biopsy of the lip lesions revealed labial lentigo compatible with this syndrome. Gastrointestinal investigation revealed a rectosigmoidal tumour. Biopsy showed an adenocarcinoma arising in an adenomatous polyp. In May he had a rectosigmoidal resection. There was carcinomatous involvement in two paracolonic lymph nodes. External beam irradiation and chemotherapy were instituted but were discontinued after a total dose of 3780 R to the abdominal area and after three intravenous injections of 800 mg 5-fluoro-2,4 (1H, 3H)-pyrimidinedione because of severe gastrointestinal symptoms. The patient noted progressive loss of vision in both eyes. In September 1988 cataract extraction failed to improve his vision.

When seen here in January 1989 he had multiple bluish brown macules of the mucous membranes of lips and mouth. They were most prominent on the inferior lip and hard palate (Fig 1). Similar lesions were present on the mucous membranes and skin of the penis (Fig 2). His family history was unknown. Visual acuity in the right eye was 1/200, left eye 20/60. There was 1+ episcleral injection bilaterally. Intraocular pressure was 10 mm Hg bilaterally. Funduscopic examination revealed ciliochoroidal elevation superiorly and temporally in both eyes. There were three slightly elevated pigmented choroidal lesions of 1 to 1·5 disc diameter size in the midperiphery of both eyes (Fig 3). There was a reticular pattern of hyperpigmentation and depigmentation of the pigment epithelium that was most evident in the macula and inferior fundi. Serous detachment of the retina was present inferiorly in the right eye.

Angiography revealed a reticular pattern of non-fluorescence on a background of marked hyperfluorescence throughout the posterior fundus and midperiphery of both eyes (Figs 4, 5). An electroretinogram showed severely abnormal rod and cone function in both eyes. Serological examinations revealed antibodies reactive with the retinal protein, cancer associated retinal antigen, at a dilution of 1:200.[5]

The patient experienced progressive loss of vision and developed three slightly raised black skin lesions in the postauricular area. In December 1989 the visual acuity in the right eye

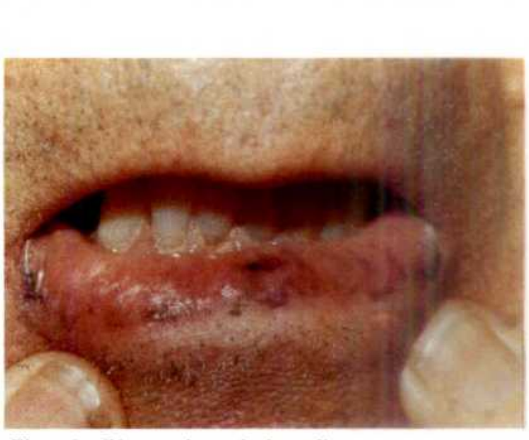

*Figure 1 Pigmented macules lower lip.*

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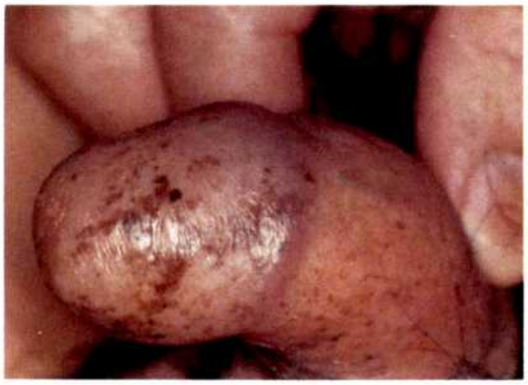

*Figure 2 Pigmented macules penis.*

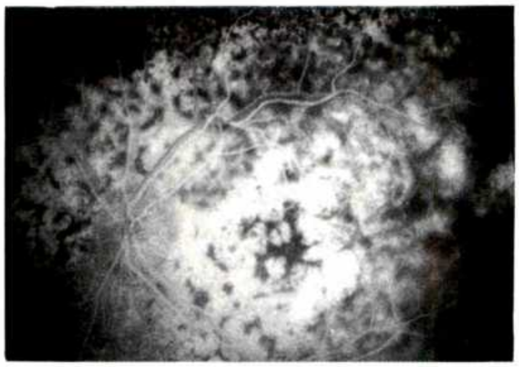

*Figure 4 Macular region. Triradiate pattern of non-fluorescence caused by clumps of subretinal pigment on background of early hyperfluorescence, indicating severe pigment epithelial damage.*

was light perception with projection and in the left eye was hand movements only. The mucous membrane lesions were unchanged. The anterior chambers were shallow peripherally. He had a mature cataract in the right eye. The intraocular pressure was 10 mm Hg in each eye. In the left eye there was a total bullous retinal detachment with shifting subretinal fluid. The pigmented choroidal lesions noted previously were unchanged. There were two new pigmented choroidal lesions in the perimacular area and extensive pigment mottling throughout the fundus. Echography revealed total retinal detachment and diffuse as well as multifocal areas of thickening of the choroid and ciliary body bilaterally.

Biopsy of the pigmented lesion of the lower lip revealed hyperpigmentation of the basal cell layer, melanocytic hyperplasia, irregular elongation of the rete ridges, and scattered melanocytes and melanophages in the underlying dermis (Fig 6). Electron microscopy revealed melanocytes containing mostly mature melanosomes interspersed among the keratinocytes. Adjacent keratinocytes displayed scattered round and oval mature melanosomes. The underlying stroma contained scattered macrophages filled with numerous melanosomes. The histopathological diagnosis was lentigo labialis. Biopsy of one post-auricular lesion revealed a pigmented basal cell cacinoma with some necrosis. In December 1989 the patient had drainage of the subretinal fluid, total vitreous replacement with silicone, and panretinal photocoagulation in the left eye.

When he was last examined, in February 1990, the visual acuity in the left eye was counting fingers at 1 m. The retina of the left eye was reattached except for a small area anterior to equator inferiorly. The pigmented mucous membrane and choroidal lesions in the left eye were unchanged. He noted no further change in his visual function or general health until June 1990, when he developed a papulonodular skin rash involving the lower trunk and legs. Biopsy revealed metastatic carcinoma to the skin.

He died in November 1990. Histopathological examination of both eyes revealed diffuse uveal tract infiltrates with apparently benign melanocytic cells in a pattern identical to that previously described.[2,4]

## Discussion

Peutz-Jeghers syndrome is an autosomal dominantly inherited disorder characterised by the association of mucocutaneous pigmented lesions and gastrointestinal hamartomatous polyps involving primarily the jejunum and ileum.[6-11] Multiple round and oval, 1 to 12 mm, blue-black or dark brown macules typically are present on the lips, particularly the lower one, and are often evident in the mucous membranes of the gums, hard palate, genitalia, and perianal region. They may also be evident on the face and hands. The lids and conjunctiva may be involved.[7,8,11] The pigmented lesions are usually present in early childhood but may develop later.[9] Those on the oral mucosa remain constant, whereas those elsewhere may often fade.

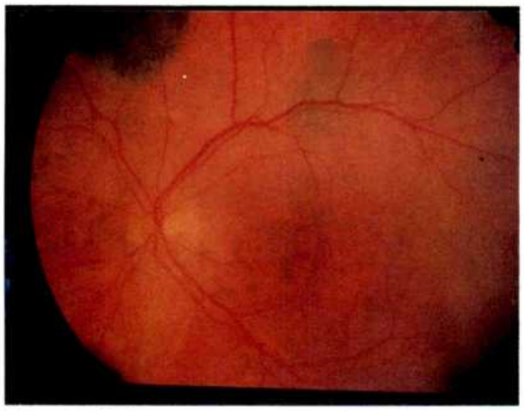

*Figure 3 Left eye.*

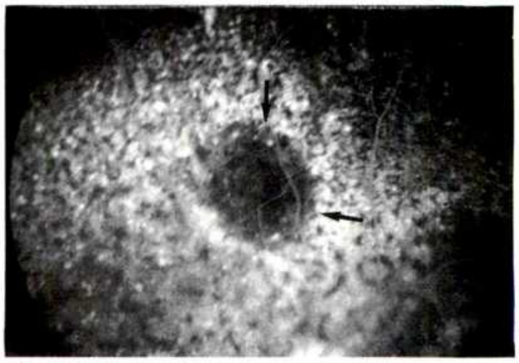

*Figure 5 Peripheral fundus (arrows indicate pigmented choroidal lesions).*

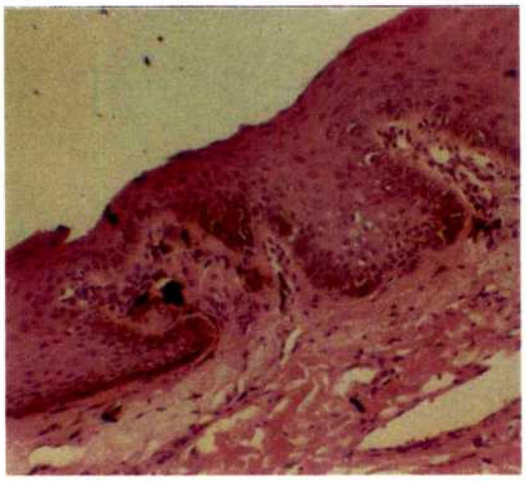

*Figure 6 Photomicrograph of lip lesions showing increased numbers of melanocytes in basal layer of epithelium and scattered melanocytes and melanophages in the dermis. (Haematoxylin and eosin, ×325.)*

Malignant change in the gastrointestinal polyps occurs in 2–3% of patients.[8]

Our patient had an occult rectosigmoid adenocarcinoma when he developed pigment oval and penile lesions that had the typical clinical and histopathological appearance of Peutz-Jeghers syndrome. Excision of the colon tumour was followed by rapid development of the typical sequence of signs and symptoms of BDUMP, including visual loss, cataracts, ciliochoroidal detachment, widespread damage to the pigment epithelium and outer retina, appearance of multifocal pigmented uveal tumours, and secondary retinal detachment. Presumably the stimulus for development of multifocal pigmented choroidal lesions and the mucocutaneous lesions was the same. Pigmented choroidal lesions developed over several months and then stabilised in spite of the patient's continuing loss of vision that was associated with progressive pigment epithelial damage and eventually secondary retinal detachment. Simultaneously, the pigmented macules of the mucous membranes and the skin stabilised.

Activation of pre-existing naevus cells by a hormone-producing carcinoma is one of the theories to explain the appearance of multifocal pigmented lesions on a background of self-limited, diffuse, amelanotic melanocytic proliferation throughout the uveal tract of patients with BDUMP.[1 4] There is histopathological evidence that development of the pigmented lesions may be more a product of cancer-induced melanin production and melanocytic necrosis than active cellular proliferation.[4] The same mechanisms may be postulated regarding the appearance of pigmented lesions in the mucous membranes and the skin of our patient. Although there are previous descriptions of BDUMP accompanied by congenital oculocutaneous melanocytosis[3] and upper respiratory melanosis,[4] our patient is the first to develop extraocular pigmentation concurrently.

This late onset of mucocutaneous pigmentation and the characteristics of this colonic cancer, though not typical of Peutz-Jeghers syndrome, do not exclude it.[7 9 10] Severe visual loss in our patient was associated with extensive pigment epithelial damage prior to development of retinal detachment, a feature noted in other cases of BDUMP. This has been ascribed to a toxic or immune reaction, initiated either by a carcinoma-uveal melanocytic interaction or directly by substances produced by the carcinoma.[4] This latter mechanism has been suggested as important in the pathogenesis of retinal damage occurring in patients who develop progressive visual loss, nyctalopia, and fundus changes simulating retinitis pigmentosa sine pigmenti in response to a systemic carcinoma, the so-called cancer associated retinopathy (CAR) syndrome.[5] Our patient had a positive assay for antibodies to retinal cancer-associated antigen. The significance of this is unknown, since a previously reported patient with BDUMP had a negative assay.[4]

No treatment has prevented severe visual loss in patients with BDUMP. Vitrectomy, silicone injection, and panphotocoagulation were successful in partly reattaching our patient's retina, but resulted in only minimal visual improvement. Perhaps this form of therapy should be considered earlier in the course of the disease.

Our patient remained free of evidence of metastasis for 26 months after the onset of his disease. He is the second patient to have survived beyond 24 months after the onset of BDUMP.[4]

Serological examinations for antibodies to cancer-associated retinal antigen were performed by Dr Charles E Thirkill.

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British Journal of Ophthalmology, 1991, 75, 696–697

# Ocular myositis as first presenting symptom of human immunodeficiency virus (HIV-1) infection and its response to high-dose cortisone treatment

Eva-Maria Fabricius, Ingo Hoegl, Wolfgang Pfaeffl

**Abstract**

**A 30-year-old male presented with signs of ocular inflammation and motility disturbances in an early stage of HIV infection. The provisional diagnosis of an ocular myositis was confirmed by orbital echograms. A general check up revealed positive anti-smooth-muscle antibodies and antinuclear antibodies as well as a raised erythrocyte sedimentation rate. Oral steroid treatment in addition to steroid eyedrops achieved complete resolution of clinical and sonographic symptoms within 15 weeks. Autoimmune phenomena are well known presentations of HIV infection. In this case oral cortisone proved to be an effective therapy even in the setting of an HIV infection.**

Various forms of myositis are known in the course of an HIV infection – for example, as a possibly rheumatic manifestation,[1] as a complication of virustatic therapy with zidovudine,[2] or as pyomyositis due to a secondary infection with bacteria[3] or protozoa.[4] Moreover, some cases of polymyositis in the early stages of HIV infection have been described in which HIV-1 itself was found in CD4-positive inflammatory cells surrounding or invading damaged muscle fibres.[5] Here we report on a patient with ocular myositis as the presenting symptom of an HIV-1 infection and its therapeutic response to high-dose cortisone therapy.

## Case report

The patient, a 30-year-old male, had already complained for a few weeks of lassitude, headache, eye related pain, swelling of the eyelids and conjunctiva, reddening of the eyes, and double vision, until he consulted us in March 1989. Treatment with antibiotic-steroid eyedrops administered up to that time had not resulted in any improvement.

On examination the visual acuity was 20/20 in both eyes. Both upper and lower lids were swollen. Apart from a tarsal conjunctivitis a slight bulbar conjunctivitis, an episcleritis, and slight conjunctival oedema were noted. The deeper eye segments were normal. In primary position the eyes were parallel. Motility testing revealed restriction of elevation and abduction of the right eye and restriction of abduction of the left eye. In the corresponding gaze directions the patient had double vision. The provisional diagnosis of an ocular myositis was confirmed by an ultrasonogram of the orbit. The patient was admitted to hospital for a general check up by electrocardiogram, chest *x* ray, cerebral computed tomogram, and a physical examination. All results were negative. Lymphadenopathy and oral candidiasis were absent. An abdominal sonogram showed no splenomegaly or enlarged abdominal lymph nodes.

Laboratory tests revealed a raised erythrocyte sedimentation rate (Westergren) of 27 mm after one hour. The differential blood count, platelets, and serum enzymes, in particular creatinine kinase, were within the normal range. Electrophoresis showed a slightly raised gammaglobulin fraction. The level of IgE was within the normal range. Tests for anti-smooth-muscle antibodies (ASMA) and antinuclear antibodies (ANA) gave positive results, whereas other autoantibodies could not be detected. A reduced CD4/CD8 ratio of 0·62, with an absolute CD4-positive cell count of $526\times10^6$/l resulted in testing for HIV infection. An enzyme linked immunosorbent assay (ELISA) test for HIV-1 antibodies showed positive results and was confirmed by Western blot. IgG antibodies in low titres were also demonstrated for Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and toxoplasmosis. The *Treponema pallidum* haemagglutinin test was negative. Other infections in stool, sputum, and blood samples were excluded.

In addition to steroid eyedrops, oral steroid treatment was started with a daily dose of 1·5 mg/kg body weight fluocortolone for five days. The initial daily dose was tapered to 0·3 mg/kg/day over the next 20 days. The clinical symptoms resolved only slowly while changing their pattern (the left superior rectus muscle became temporarily paretic, and the episcleritis affected different locations of the bulbus before it resolved), so that the patient was maintained on this daily dose for another six weeks. After a further five weeks on a daily dose of 0·12 mg/kg body weight fluocortolone the systemic treatment was stopped, when complete resolution of the clinical symptoms was achieved and the sonographic controls of the eye muscles were normal (Fig 1).

Since then, after a follow-up of 15 months, the patient has remained free of symptoms without any therapy. He had received a cumulative dose of 2780 mg of fluocortolone over a period of 15 weeks without suffering any infectious complications by the potential immunosuppressive effect of cortisone and the underlying HIV-1 infection.

## Discussion

The pathogenesis of HIV associated myositis is not entirely clear. Apart from an invasion of the musculature by HIV infected inflammatory cells[5] our case of ocular myositis perhaps sug-

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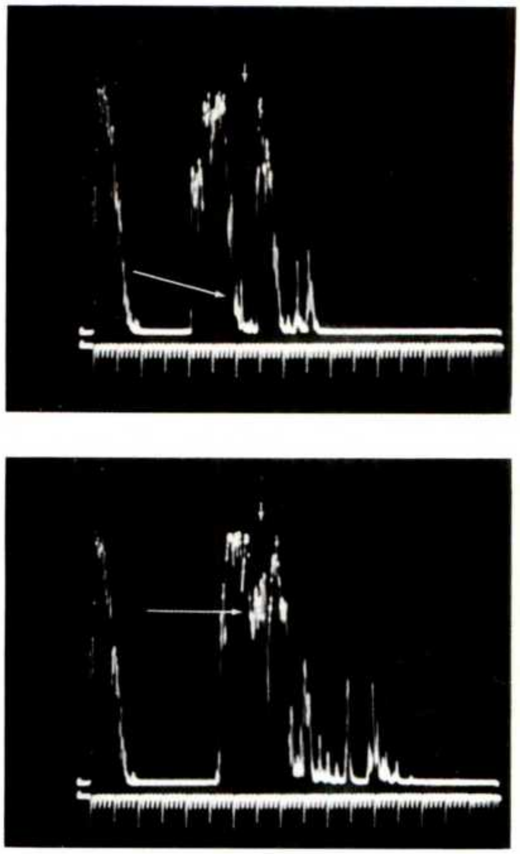

*Figure 1 Standardised A-scan echograms of the orbit in ocular myositis (G Hasenfratz, Department of Ophthalmology, Ludwig-Maximilians-University of Munich). Top (5 April 1989): Acute myositis: broadening (short arrows) of the muscle insertion region and massive broadening in the region of the belly of the muscle with appreciably lowered reflectivity of the muscle tissue and a homogeneous internal structure (long arrow). Bottom (6 June 1989): Decline of the muscle broadening (short arrows) and rise of the muscle reflectivity (long arrow) after systemic steroid therapy.*

gests an autoimmune mechanism. Autoimmune phenomena are well known presentations of the HIV infection. In HIV infection autoantibodies against lymphocytes,[6] platelets,[7] nerve tissue,[8] and other cell structures have been demonstrated. They are signs of the complex loss of a normal immune regulation in these patients. Polymyositis as the initial manifestation of HIV infection has been recognised,[5 9] but to the best of our knowledge this is the first report of an ocular myositis as the first presenting symptom of HIV infection. The presence of autoantibodies and good therapeutic response to cortisone in our case supports an autoimmune mechanism. Normal muscle enzymes in HIV associated myositis have been observed.[10] In our patient high dose oral cortisone proved to be an effective therapy even in the setting of an HIV infection.

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# Intraocular involvement with subretinal pigment epithelium infiltrates by mycosis fungoides

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## Abstract

**We report a case of intraocular mycosis fungoides in a 48-year-old man. The patient presented with decreased visual acuity, white subretinal lesions, and vitritis. Post-mortem histopathology revealed malignant T cell infiltrates consistent with mycosis fungoides in the retina, vitreous, and between the retinal pigment epithelium (RPE) and Bruch's membrane. Focal atrophy of the RPE, along with the sub-RPE infiltrates, correlated with the clinically visible fundus lesions.**

Mycosis fungoides is a cutaneous T cell lymphoma, which can progress to generalised disease.[1] It commonly presents with a long phase of 'premycotic' skin lesions. These progress to patches on the skin, which may or may not become plaques, and eventually tumours.[2] The clinical course of skin involvement varies from chronic to rapidly progressive, and is unpredictable.[3] Systemic involvement is late in the course of the disease, and usually involves the lymph nodes, liver, spleen, and/or central nervous system.[4] Because the majority of patients develop the disease between the ages of 40 and 60, many of them die of unrelated causes before the disease becomes widespread.

Eyelid and conjunctival involvement is not unusual in the course of mycosis fungoides.[5] Other external ocular involvement has been reported, including cornea,[6] caruncle,[7] sclera,[6] and orbit.[8] Intraocular lesions are rare, and only a few individual cases have been reported. Only one of the previous reports records both the clinical and pathological appearance of intraocular mycosis fungoides.[9]

We present here a patient followed up closely for an ocular disease that resembled fungal endophthalmitis but was histologically proved to be mycosis fungoides.

## Case report

The patient was a 48–year-old white man known to have had mycosis fungoides for 30 years. He had disseminated skin lesions for which he received topical steroids, psoralen and ultraviolet light (PUVA), superficial *x* ray therapy, and in 1989 intermittent oral chlorambucil (Leukerad). In 1983 he had undergone surgery for a subarachnoid haemorrhage.

On 1 November 1989 the patient complained of blurring of vision mainly in the left eye. Ophthalmic examination revealed bilateral disc swelling and small white lesions in the fundus (Figs 1A, B. The disc swelling resolved spontaneously. Four weeks later his vision dropped to 6/12 in the right eye and counting fingers in the left. The left eye showed anterior uveitis, and severe vitritis with active retinitis in the posterior pole (Fig 2). The left eye had also developed a conjunctival perilimbal nodular yellow infiltrate (Fig 3). A presumed diagnosis of candida chorioretinitis was made, and the patient was treated with intravitreal amphotericin and oral ketoconazole. Cultures and stains of vitreous biopsies were negative, and oral ketocanazole was continued. By 5 December the right eye also developed a small white lesion in the macula (Fig 4), a limbal lesion, and conjunctival infiltrates.

At the same time the patient was admitted to hospital for control of pain and a newly discovered left sided abdominal mass. He died on 21 December 1989, with a diagnosis of mycosis fungoides and widespread lymphoma.

### POST MORTEM FINDINGS

The body was covered with numerous crusting skin lesions up to 2 cm in diameter. There was evidence of extensive involvement of the lymph nodes by lymphoma, which also appeared to be infiltrating retroperitoneal tissues.

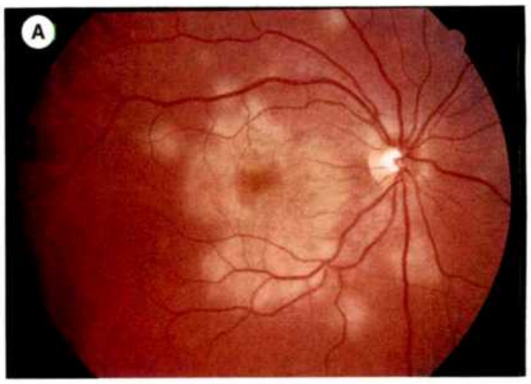

*Figure 1A*

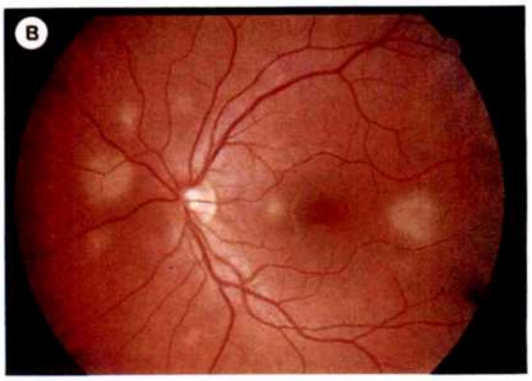

*Figure 1B*

*Figure 1 Fundus, left eye. A Small circumscribed white subretinal lesions were seen throughout the mid periphery of the retina. B There was one lesion in the macula.*

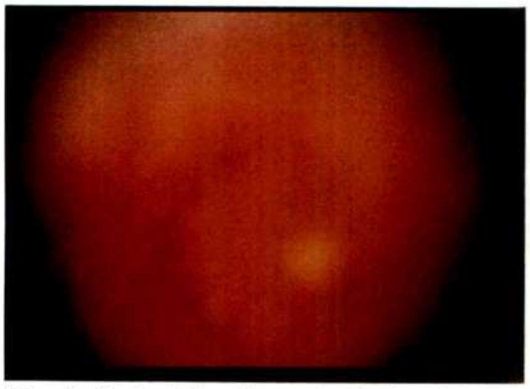

*Figure 2 Fundus, left eye. Four weeks after the retinal lesions were first observed the patient developed vitritis with active retinitis.*

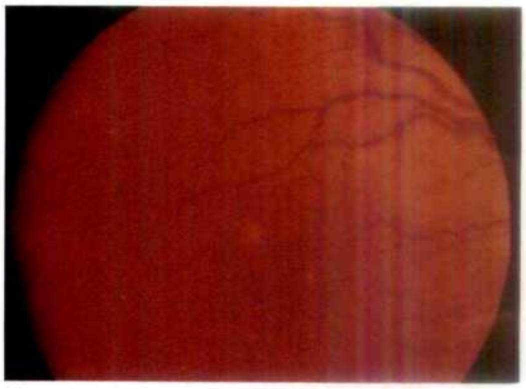

*Figure 4 Fundus, right eye. Small white subretinal lesion in the macula.*

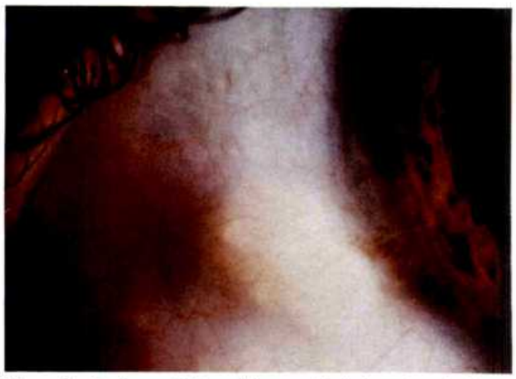

*Figure 3 Left eye. This nodular perilimbal conjunctival infiltrate was noted four weeks after the patient's initial eye examination.*

Microscopically the dermis displayed a diffuse infiltrate of small lymphocytes plus occasional larger cells with bizarre hyperchromatic nuclei. In some areas there was infiltration into the epidermis, though discrete microabcesses were not identified. There was heavy lymphoid infiltrates within the cortex of the left kidney which extended to the surface and infiltrated perinephric tissues. A similar lymphoid infiltrate was seen in the myocardium and testis. Lymph nodes from the periaortic region also showed effacement of the architecture by a similar infiltrate, which extended widely into the surrounding fatty tissue. Immunocytochemical markers indicated that the infiltrate was predominantly composed of T lymphocytes.

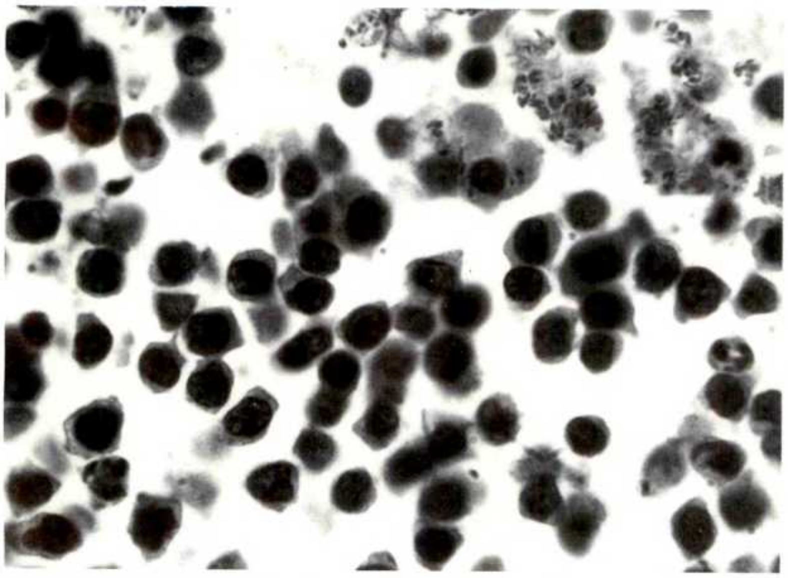

*Figure 5 Lymphomatous infiltrate beneath the RPE contains cells with scanty cytoplasm and large pleomorphic nuclei with convoluted borders, consistent with mycosis fungoides. (Haematoxylin and eosin, ×400.)*

The histological appearances were consistent with a T cell lymphoma arising in mycosis fungoides and leading to diffuse visceral infiltration.

### OCULAR HISTOPATHOLOGY

Both eyes showed similar findings, these being more pronounced in the left eye. Anteriorly the eyes were normal. The striking feature in the posterior segment was the presence of abnormal lymphocytes, which were consistent with mycosis fungoides, between Bruch's membrane and the retinal pigment epithelium (RPE). The cells had scanty cytoplasm and large pleomorphic nuclei with convoluted borders (Fig 5). The infiltrate formed a diffuse layer, 1 to 15 cells thick, under the equatorial and peripheral RPE, and also extended a short distance under the pars plana epithelium. The thickness of this infiltrate varied throughout the specimen and often changed abruptly from sparse to dense. The overlying RPE showed variable focal degeneration and atrophy (Fig 6). The retina contained loose focal infiltrates of lymphomatous cells in the nerve fibre layer and ganglion cell layer, particularly round the retinal vessels (Fig 7). The outer retinal layers were normal. The choroid had a mild diffuse infiltrate of similar abnormal lymphocytes (Fig 8). Lymphomatous cells also infiltrated the small amount of vitreous base which remained after the vitrectomy (Fig 9). The ciliary body, iris, and episclera contained a slight lymphocytic infiltrate but no large lymphoma-like cells.

The optic nerve and conjunctiva were not available for examination.

### IMMUNOHISTOPATHOLOGY

The isolated cell population found between the RPE and Bruch's membrane was studied further by immunoperoxidase stains on paraffin sections. There was a positive reaction for the leucocyte common antigen (PD7) and two pan-T cell markers (L60, A6). The pan-B marker (L26) was non-reactive, which would be unusual in a benign lymphoid infiltrate. Therefore the find-

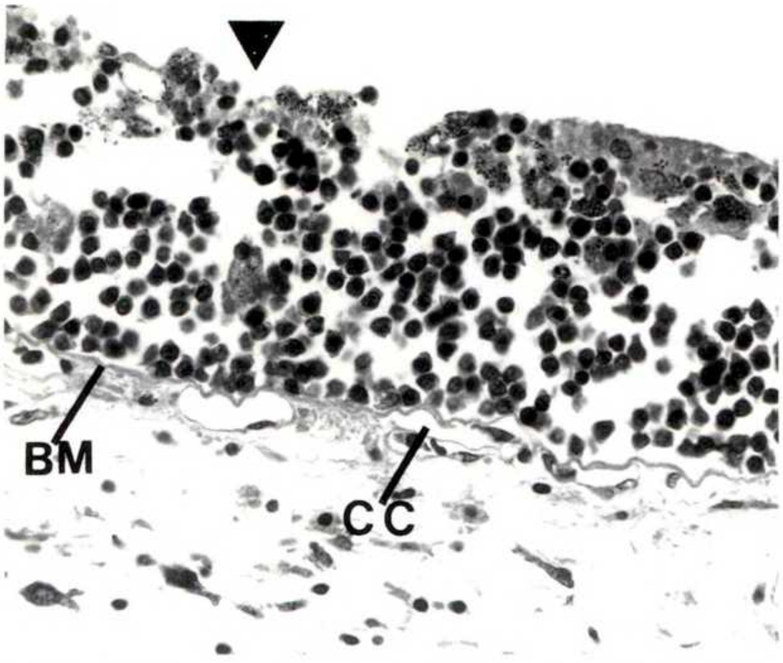

*Figure 6 The infiltrate forms a diffuse layer of lymphomatous cells under the RPE. In this area the infiltrate is thick. The overlying RPE exhibits variable focal degeneration and atrophy (arrowhead). Bruch's membrane (BM) is intact, and the choriocapillaris (CC) is normal. (Haematoxylin and eosin, ×200.)*

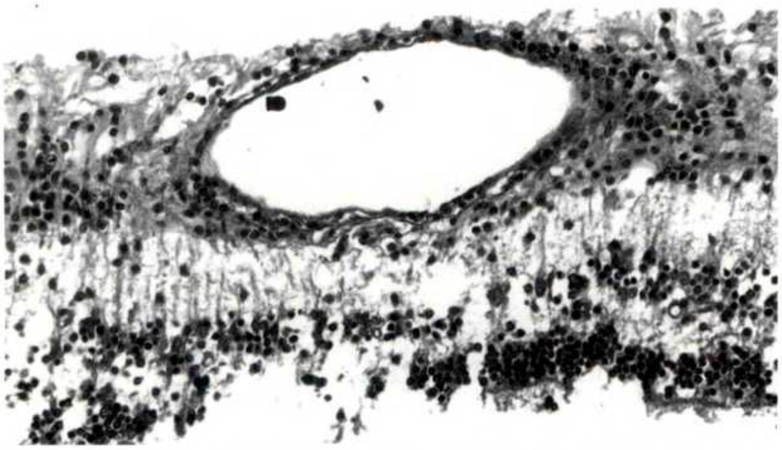

*Figure 7 The retina contains loose focal infiltrates of lymphomatous cells in the nerve fibre layer and ganglion cell layer, here shown concentrated around a retinal vessel. (Haematoxylin and eosin, ×200.)*

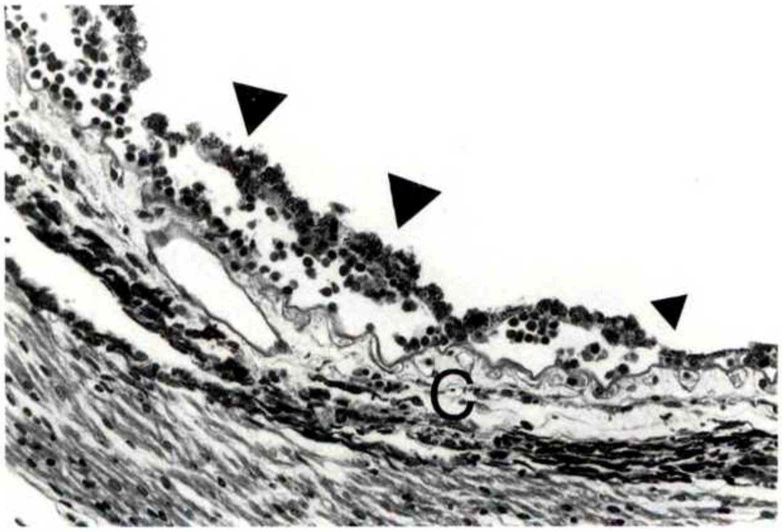

*Figure 8 In this area there is a thin infiltrate of lymphomatous cells beneath the RPE (large arrowheads) and beneath the epithelium of the pars plana (small arrowhead). The choroid (C) contains a scanty lymphomatous infiltrate. (Haematoxylin and eosin, × = 100.)*

ings indicated exclusive T cell proliferation consistent with involvement of the eye by micosis fungoides.

## Discussion

Intraocular involvement of mycosis fungoides has been rarely reported. Gartner[10] reported the first known case, in which the choroid was infiltrated with neoplastic cells. Hogan[11] presented a case in which the uvea was infiltrated with neoplastic cells and the optic nerve had tumour anterior to the lamina, which extended to the adjacent retina. Keltner *et al*[9] described a patient with involvement of the central nervous system and eyes in whom at necropsy mycosis fungoides cells were found in the retina, optic disc, and vitreous. Foerster[12] presented a case and described the pathological finding of neoplastic cells forming a diffuse layer beneath the RPE, as seen in the present case. Intraocular involvement has been noted only in the end stage of the disease in all of these cases: from 17 days[11] to one year before death.[12] In our patient the eye involvement was discovered seven weeks before his death.

In this paper we present a case of mycosis fungoides with clinical and pathological correlates of the intraocular involvement, which most strikingly includes infiltrates between the RPE and Bruch's membrane. In our sections it appears that cells have arrived in the sub-RPE potential space by crossing Bruch's membrane from the choroid. Barr *et al*[13] reported two cases of similar lesions in large cell lymphoma. This finding suggests that lymphocytes from various lymphomas may have a predilection to accumulate in the sub-RPE space. The retinal perivascular infiltrates and vitreous metastases are similar to those reported by Keltner *et al*[9] Metastases to the retina characterised pathologically by collarettes of tumour cells surrounding retinal vessels, evidently occur by haematogenous spread, as has also been reported in leukaemia.[14]

The lesions in our patient clinically mimicked candida chorioretinitis, with white retinal spots and overlying vitreous haze. However, the histopathology shows that the white spots are focal atrophy of the RPE and accumulation of lymphomatous cells beneath the RPE. Patients with mycosis fungoides are not particularly susceptible to candida infection unless they are immunocompromised from chemotherapy, or have other risk factors.[15]

Ophthalmologists asked to see patients with extracutaneous mycosis fungoides need to consider strongly the possibility of intraocular malignancy. Radiotherapy has successfully treated an orbit infiltrated by mycosis fungoides.[16] There has also been a report of focal radiotherapy to an involved caruncle with complete resolution.[7] Perhaps focal radiation to the retina and choroid could be given in an attempt to preserve vision in patients with intraocular mycosis fungoides.

Supported in part by unrestricted funds from the Research to Prevent Blindness.

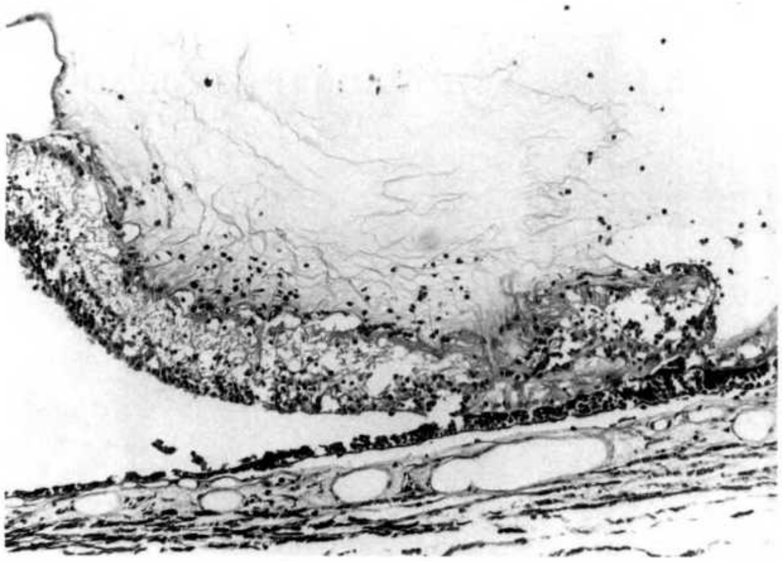

*Figure 9 Lymphomatous cells are seen infiltrating the remaining vitreous at the vitreous base adjacent to the ora serrata. (Haematoxylin and eosin, ×40.)*

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*British Journal of Ophthalmology*, 1991, **75**, 702–703

# *Oestrus ovis* ophthalmomyiasis acquired in the UK: case report and scanning electron microscopic study

J D Stevens, A C E McCartney, R Howes

**Abstract**

**A case of external ophthalmomyiasis acquired in the UK is reported. *Oestrus ovis* infestation of the external conjunctiva is described and a scanning electron microscopic study made of the first stage larvae. To our knowledge this represents only the third case reported of UK acquisition of ophthalmomyiasis.**

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Accepted for publication 25 April 1991

A 32-year-old woman with no past ophthalmic history attended Moorfields Eye Hospital complaining that she had been sunbathing in her garden in Dorset in August when she felt a foreign-body sensation in her right eye which persisted after a fly had landed on her closed right eyelid. She was aware that she had some difficulty in brushing the fly away, and began to experience an agonising moving foreign-body sensation in the eye. She looked in a mirror and saw moving larvae and managed to remove four larvae before attending Moorfields Casualty Department later the same day.

Examination revealed three larvae moving on the surface of the conjunctiva. These were transparent, segmented, and anteriorly had black mouth parts. They were removed with a moistened cotton bud. The larvae displayed negative phototaxis, moving away from the slit-lamp light beam. The tarsal conjunctiva was mildly inflamed. There was no evidence of subconjunctival penetration by the organisms, and none was seen in the anterior or posterior chambers of the eye. Two larvae were kept for species identification and scanning electron microscopy. Treatment with prednisolone eyedrops 0·3% and chloramphenicol eyedrops four times daily was given. Review next day revealed mild irritation and a follicular conjunctival response but no further feeling of movement.

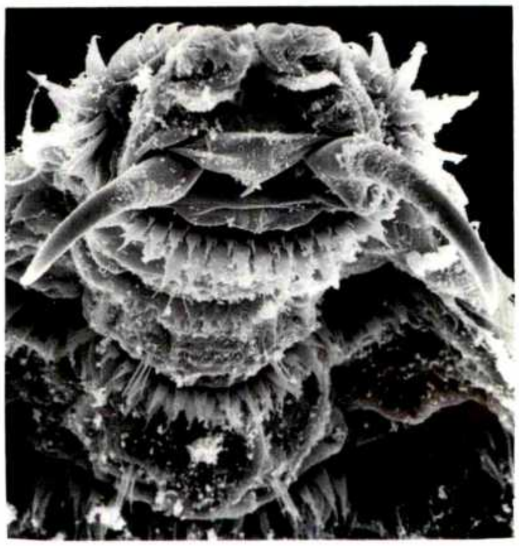

*Figure 2 Enlarged view of anterior end showing mouthpiece. (×340.)*

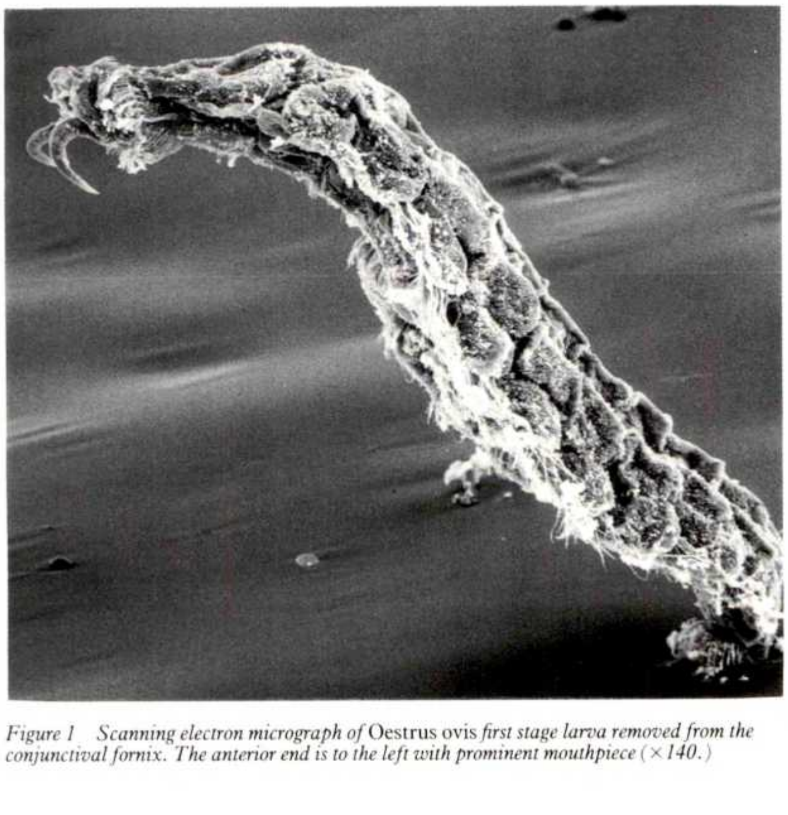

*Figure 1 Scanning electron micrograph of* Oestrus ovis *first stage larva removed from the conjunctival fornix. The anterior end is to the left with prominent mouthpiece (×140.)*

However, a new symptom of unilateral sneezing developed. Examination of the nasal passages revealed no organism and the rhinitis resolved over the next three days. On follow-up an ocular examination gave normal results.

The specimens were identified as first stage larvae of *Oestrus ovis* by Dr R G Adams of the Ministry of Agriculture, Fisheries, and Food.

## Discussion

Ophthalmomyiasis is a condition in which the eye is invaded by larvae of the order Diptera. When larvae remain outside the eye it is termed ophthalmomyiasis externa, while penetration of the anterior or posterior chamber of the eye is termed ophthalmomyiasis interna.[1] Eighty species of Diptera have been known to invade man.[2] *Oestrus ovis*, the sheep nasal bot fly, has been reported from the Mediterranean,[3] Asia, and the Americas,[4] reflecting the distribution of sheep. Ophthalmomyiasis acquired in England has been reported before but is very rare. In 1950 *Oestrus ovis* was reported in England,[5] possibly being acquired in Devon, and one other case is currently being reported from Portsmouth.

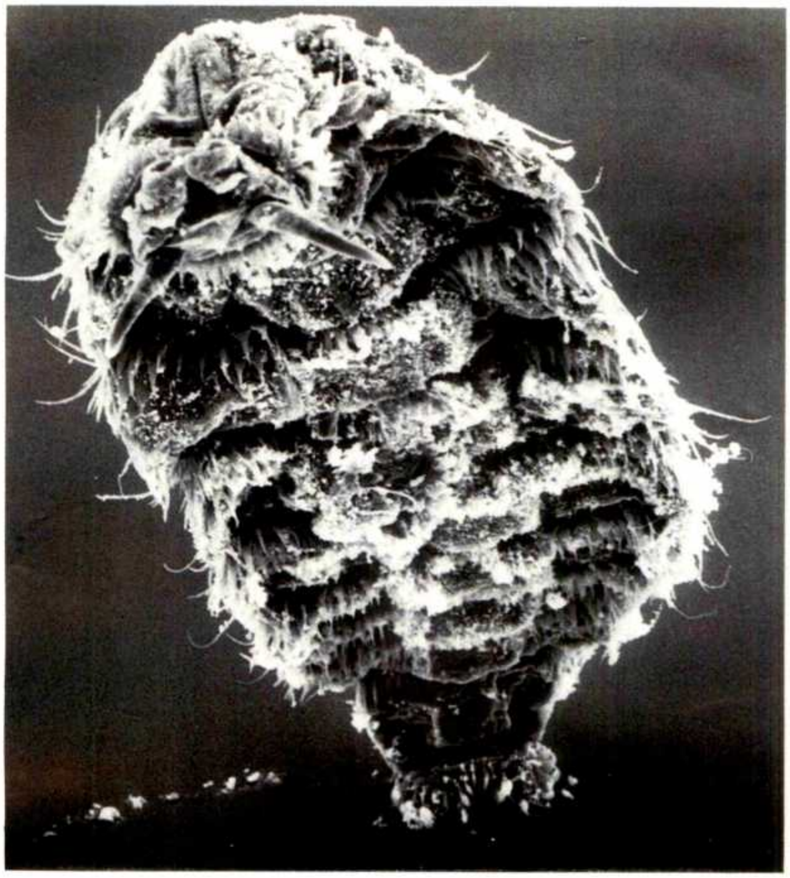

*Figure 3 Anteroposterior view showing underside of larva. (×140.)*

Infestation by larvae has also been reported from the New Forest, Hampshire.[6] Larvae may otherwise be imported into the UK.[7]

During the summer gravid adult females deposit their maggots on the nares of sheep and goats. Occasionally humans may become the target, and larvae may be directly deposited on the conjunctiva. The symptoms are of acute conjunctivitis,[8,9] with soreness, lacrimation, and conjunctival injection. There may also be a follicular conjunctival reaction.[10] The larvae are relatively harmless if removed promptly, and *Oestrus ovis* does not burrow, so infestation is limited to the outer membranes of the eye. The larvae cannot mature on the human conjunctiva, and they soon die. However, *Hypoderma* may penetrate the eye and cause profound damage.[11] The infection of the conjunctival sac by fly larvae is rare in Western Europe but is commoner in Eastern Europe and the tropics. The symptom of rhinitis in association with the conjunctival reaction has been reported before.[10] In our case no organisms were seen on nasal examination.

The help is acknowledged of Dr R G Adams, Storage Pests Department, Insect Identification Unit, ADAS Central Science Laboratory, Ministry of Agriculture, Fisheries and Food, London Road, Slough SL3 7HJ.

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# LETTERS TO THE EDITOR

### Herpes simplex keratitis in renal transplant patients

SIR, – I read with interest the paper by Kremer *et al.*[1] In particular I was intrigued by their observation that the epithelial herpetic lesions in these patients were located mainly in the periphery of the cornea and responded poorly to routine therapy. Additionally there was no stromal involvement in this small group of patients.

We recently reported[2] several cases of herpetic epithelial keratitis in patients with acquired immune deficiency syndrome (AIDS). Similarly in this group of patients there was a preponderance of peripheral corneal involvement. Additionally these lesions were somewhat recalcitrant to routine antiviral therapy. Furthermore we have not observed any AIDS patients with herpetic stromal keratitis.

It was of great interest that the clinical courses of patients with herpetic keratitis who also happen to have either AIDS or immunosuppression following renal transplantation is so strikingly similar. It is particularly intriguing that in both groups of patients there appears to be a lack of stromal involvement, perhaps indicating a role for cellular immunity in the development of stromal herpetic keratitis. The potential role of cellular immunity in the pathogenesis and treatment of epithelial herpetic keratitis is much less clear, but certainly the similar clinical appearances in these two groups of patients is suggestive.

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*Department of Ophthalmology,*
*1855 West Taylor Street,*
*Chicago, Illinois 60612, USA*

1 Kremer I, Wagner A, Shmuel D, *et al.* Herpes simplex keratitis in renal transplant patients. *Br J Ophthalmol* 1991; 75: 94–6.
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SIR, – In reply to the letter of Dr Jeffrey B Robin the similarity between the clinical picture of our renal transplant patients and that of the AIDS patients described by Young *et al*[1] and by Dr Robin is very interesting. In my opinion it is an important contribution to the understanding of the immunopathology of herpetic corneal disease. More attention should be directed to herpetic keratitis in these immunosuppressed patients and the rarity of stromal disease should be reinforced by long term follow up studies.

ISRAEL KREMER
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*Sackler School of Medicine,*
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*Israel*

1 Young T, Robin JB, Holland GN, *et al.* Herpes simplex keratitis in patients with AIDS. *Ophthalmology* 1989; **96**: 1476–9.

# OBITUARY

## E G ATKINSON, *MBChB, MSc, MRCP*

Edmund Atkinson had just resumed his clinical training in ophthalmology, after three years in research, when he died in a paragliding accident in France in June 1990. He had been an invaluable and enthusiastic member of the retinal vasculitis research group at St Thomas's Hospital, and presented his work both at the OSUK and ARVO. He qualified in medicine at Bristol University in 1982, and obtained his MRCP after working in local hospitals. He then moved to London to start his career in ophthalmology at St Bartholomew's Hospital. As he wished to develop his research interests as soon as possible he moved to St Thomas's Hospital, where in 1986 he became an MRC Training Fellow. He developed two new animal models of uveitis, and extended earlier work on its pharmacological modulation. Later he worked with the pharmacology department to develop FITC-dextran angiography as a method for investigating permeability changes in human uveitis. At the time of his death, he was continuing his studies on cloning vitreous T-cells from uveitis patients. He was always a potent source of ideas, support, and enthusiasm and always wished to stretch his many talents to the full. It was tragic that his latest enthusiasm should also be the cause of his early death.

CE

# BOOK REVIEW

**Ophthalmologische Ultraschall diagnostik; mit Atlas, Standardisierung und Einordnung in den augenärztlichen Untersuchungsgang.** Eds Herausgegeben von W Buschmann, H G Trier. Pp 494. DM 240.00. Springer: Heidelberg, 1989.

This comprehensive and definitive textbook on ultrasound diagnosis covers the subject in great depth and detail. The editors have commissioned contributions from 30 authors, most of whom have international reputations in the field of ultrasonography and its allied techniques. The result is a beautifully produced and well illustrated book but unfortunately one that will be heavy going for the average clinician and a non-starter for those who do not speak German, since there are sadly no English translations or summaries. It is a book therefore for the experts, and even they may be disappointed, because it is expensive, and in a rapidly expanding subject such as ultrasonography they are entitled to expect the references to be more up to date.

T J FFYTCHE

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# NOTES

### Hong Kong Ophthalmological Society

The Annual Scientific Meeting of the Hong Kong Ophthalmological Society will be held from 30 November to 1 December 1991 in Hong Kong. The main topic will be 'The eye and systemic diseases'. Further details from: The Secretariat, Annual Scientific Meeting 1991, Hong Kong Ophthalmological Society, c/o The Hong Kong Medical Association, 5/F Duke of Windsor Building, 15 Hennessy Road, Hong Kong. (Tel: (852) 5278285 (4 lines). Fax: (852) 8650943.)

### Wilmer Ophthalmological Institute

The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions will sponsor the following continuing education programmes.

Management of Diabetic Retinopathy: Application of Guidelines from 1991 ETDRS Publications on 15 November 1991 at the Thomas B. Turner Building, Johns Hopkins Medical Institutions, Baltimore, Maryland.

4th Annual Current Concepts in Ophthalmology plus Hands-On Excimer Laser and Phacoemulsification Wet Labs on 12-14 December 1991 at the Thomas B. Turner Building, Johns Hopkins Medical Institutions, Baltimore, Maryland.

Recent Advances in the Management of Age-Related Macular Degeneration: Guidelines from Recent Clinical Trials on 25 January 1992 at the Thomas B. Turner Building, Johns Hopkins Medical Institutions, Baltimore, Maryland.

14th Annual Current Concepts in Ophthalmology plus Hands-On Phacoemulsification Wet Lab on 9–16 February 1992 at the Hyatt Regency Cerromar Beach Hotel, Dorado, Puerto Rico.

9th Annual Current Concepts in Ophthalmology plus Hands-On Phacoemulsification Wet Lab on 14–21 March 1992 at the Manor Vail Lodge, Vail Colorado.

Laser Technology in Retinal Diseases – Current Concepts on May 16, 1992 at the Thomas B. Turner Building, Johns Hopkins Medical Institutions, Baltimore, Maryland.

Retinal Pigment Epithelium in Health and Macular Degeneration: A Symposium for Clinicians and Basic Scientists on 5–6 June 1992 at Stouffer Harborplace Hotel, Baltimore, Maryland.

Further information: Program Coordinator, Johns Hopkins Medical Institutions, 720 Rutland Avenue, Turner 20, Baltimore, Maryland 21205–2195, USA. (Tel: (301) 955–2959.)

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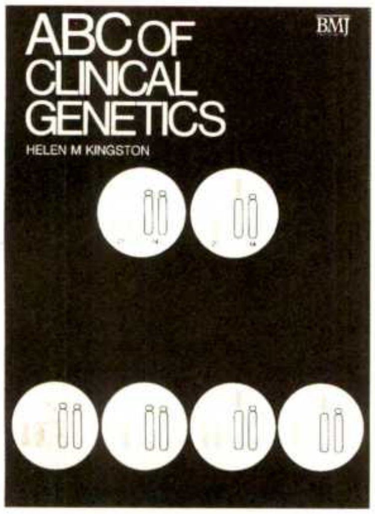

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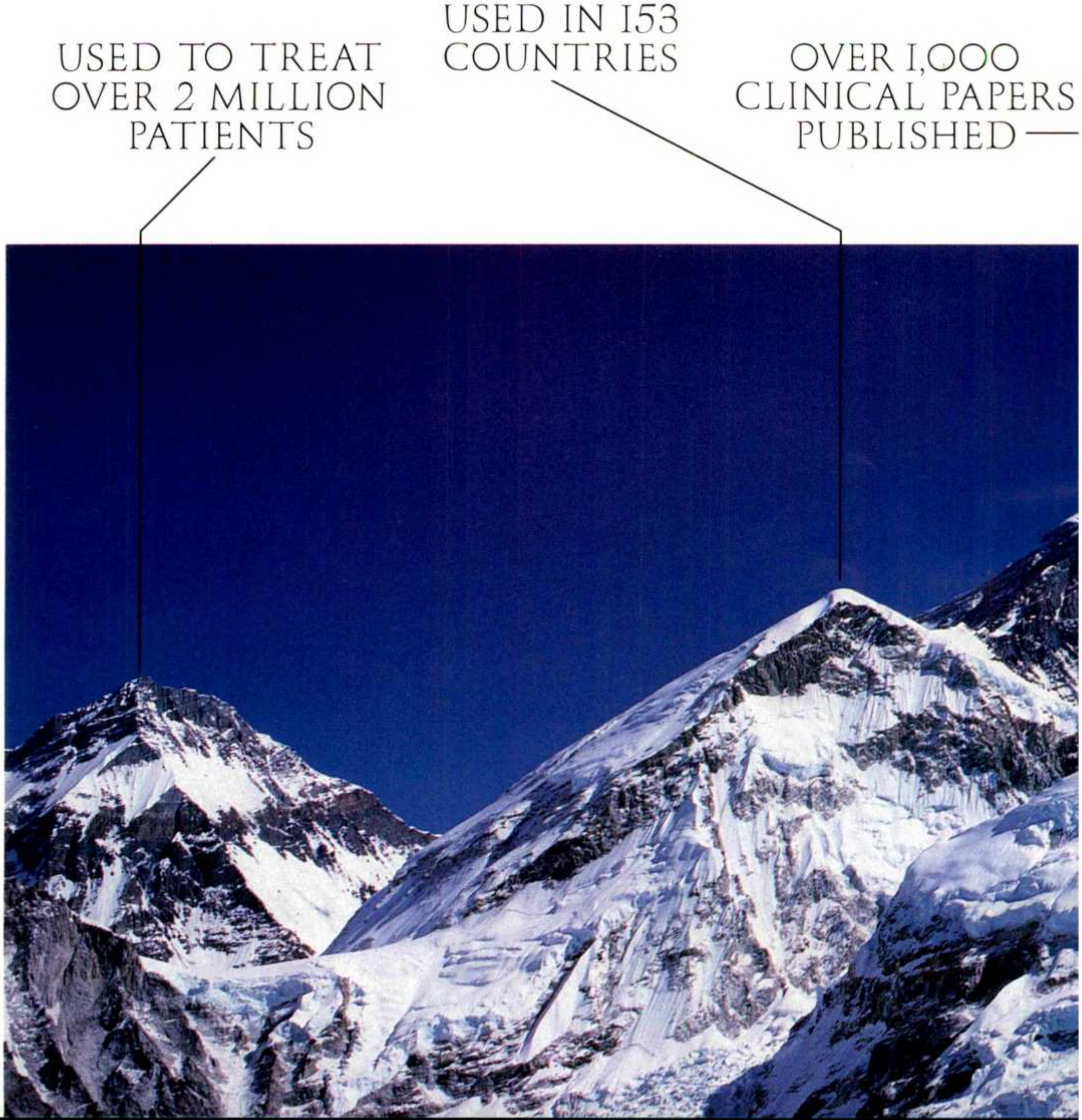
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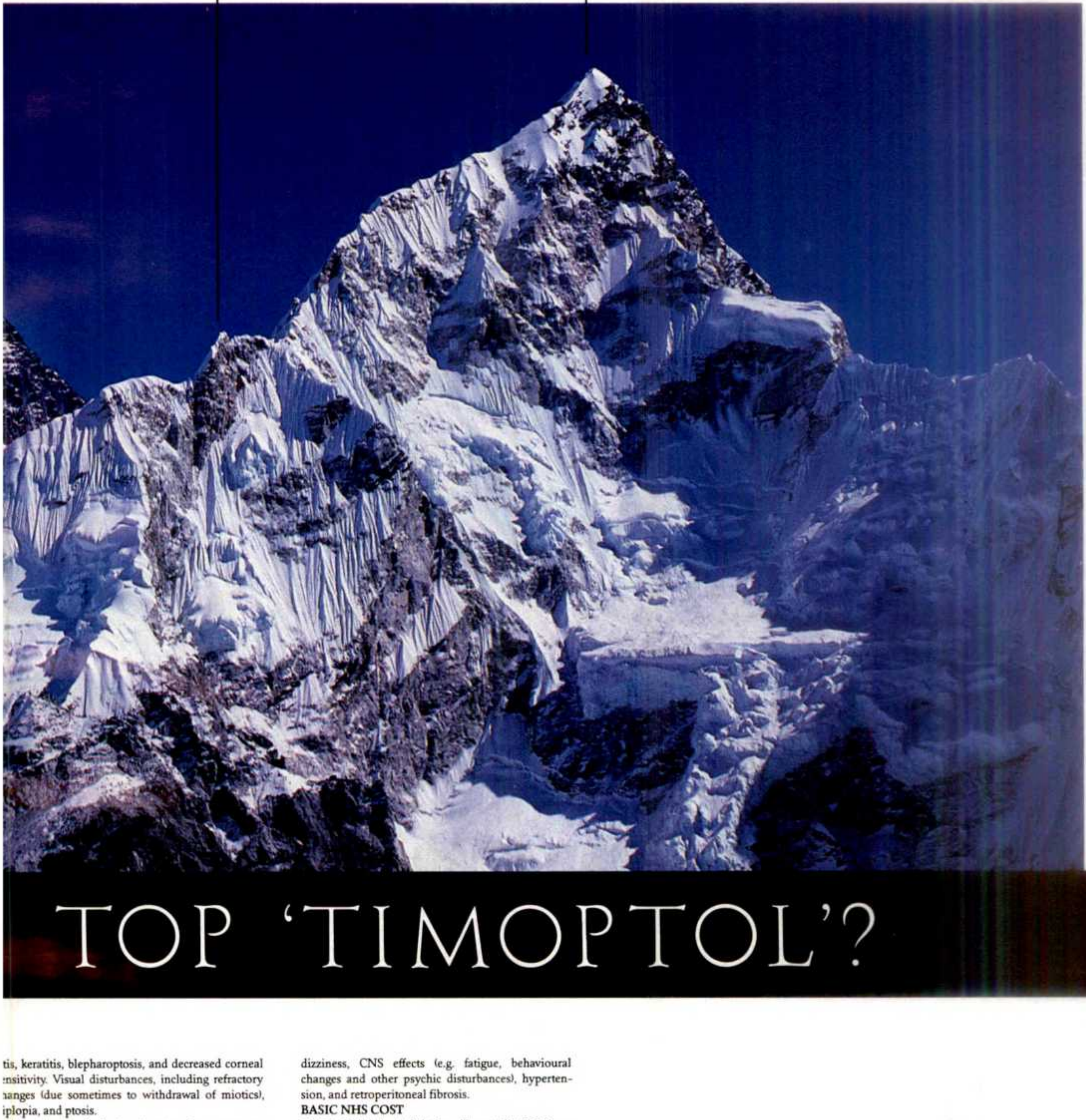

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## *Editorial*

# Christmas Editorial 1991

Two years have elapsed since the *BJO* appeared in its new form. During this time the editor has received a few comments from readers – most of them favourable; people seem to like the new layout. The first wave of mini-reviews appears also to have been appreciated and a new series is now being assembled. Would-be authors need not be shy in offering mini-reviews but, as with original papers, acceptance can be by no means guaranteed.

Speaking of original papers perhaps a word or two of information might be of interest to readers. The number of papers submitted to the journal has increased during the past year. There was a time two or three years ago, when our publication delay extended to almost two years, when new papers began to dry up. This certainly helped the publication delay as there was a period when very few papers were accepted without any notable ones having to be turned down. Because of the recent increase in the number of papers submitted however, the position has now been reached where all suitable papers cannot be accepted without the publication delay lengthening again, so that the polite rejection of a paper on the grounds of 'no room' is now no longer a courteous way of saying that a paper is not up to standard but may be literally true.

How therefore can authors maximise their chances of acceptance? There is an excellent article on the subject by Frank Newell with reference to acceptance by the *American Journal of Ophthalmology*[1] and would-be authors are certainly advised to consult this since all it says about the needs of the *AJO* applies equally to the *BJO*. In addition to following Frank Newell's excellent advice our instructions to authors, printed on the inside of the front cover, should of course be adhered to as well. It is surprising how many authors fail to have their manuscripts decently typed in reasonably good English, together with a copy. Loss between the office and the referee can occasionally occur and if there is no copy considerable delay, if not complete disaster, is inevitable. Although it is not printed in the 'instructions' common sense would dictate that authors number their pages so that the referee can refer to a query on page x line y, etc, but it is amazing how many authors fail to number the pages. (A specific request for this is to be added to the instructions.) Obviously this sort of thing will not get a paper rejected if the scientific content is satisfactory but in a competitive situation every little helps; an irritated referee is not an author's best friend.

As far as the content is concerned what one seeks first is originality. There is little point in publishing material, however carefully worked up and beautifully presented, if the average reader is likely to know about it already. Thus although scientific validity, correct statistical analysis, and excellent illustrations are all highly desirable, the paper that is most favoured is one which, ophthalmologically speaking, is news. One or two snags crop up regularly and may prejudice prompt acceptance.

An example is the pitfall of using statistics based on populations of 'eyes' as opposed to patients especially where some are the right and left eyes but others single eyes from individual patients. Significance levels based upon such populations are likely to be distorted by the fact that the pairs of eyes are not true independent variables.[2]

Such mixed populations need special statistical treatment. The simplest way is to use only one eye from each patient by some form of random selection, or sometimes by splitting the study into right and left eyes. Under some circumstances averaging the results of a pair of eyes will do but the essential thing is that the 'n' number in any calculation should not exceed the number of patients in each study.

It remains for me to wish all *BJO* readers a Happy Christmas and it is hoped that readers will not be affected by prandial presbyopia as they peruse their *BJO*s during Christmas dinner (see the paper in this issue by Hudson *et al*).

REDMOND SMITH

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## *Editorial*

# *Propionibacterium acnes* endophthalmitis

Acute postoperative infectious endophthalmitis is one of the most serious complications of cataract surgery. Its poor visual prognosis justifies the adoption of an aggressive management approach. This includes obtaining immediate specimens of vitreous and aqueous for microscopic examination and culture, removing the bulk of the infectious agent by vitrectomy, and injecting intracameral antibiotics to which the causative organism is susceptible. With this approach useful vision may be salvaged.[1]

In 1976 the first report of postoperative endophthalmitis caused by *Propionibacterium acnes* appeared in the *American Journal of Ophthalmology*.[2] The authors had applied the protocol for investigating immediate postoperative infection to eyes with chronic relapsing low grade inflammation and had isolated this organism from the eye of a patient with suspected fungal endophthalmitis.

Subsequent reports have described a typical clinical picture.[3] A granulomatous uveitis presents weeks or months after uneventful extracapsular cataract surgery sometimes associated with hypopyon and with white plaques on the posterior capsule. It is initially responsive to topical steroids, but the inflammation recurs as soon as the steroids are withdrawn. Biopsy of vitreous, aqueous, or capsular bag contents have grown *Propionibacterium acnes*, a ubiquitous Gram positive bacillus which is grown on anaerobic culture of swabs from normal human conjunctiva.[4]

I am sure that most of us can recall patients who present with late onset uveitis in the operated eye. It is worrying to wonder how many of these might have been harbouring *Propionibacterium acnes* in their capsular bags. Despite the above reports there remains a natural hesitation to submit these eyes to further surgery. Most of us rely initially on a course of topical steroids to suppress the inflammation. The majority of cases reported so far appear to justify this approach. The treated eyes of patients with culture positive *Propionibacterium* endophthalmitis achieve a reasonable final visual acuity in spite of an initial delay in diagnosis and treatment.

If the inflammation persists despite the topical steroids vitreous samples must be taken. These should be submitted to extensive bacteriological investigation maintaining anaerobic cultures for a minimum of 9 days.

Postoperative inflammation is not a new phenomenon in extracapsular cataract surgery. It has been attributed to many different causes,[5] for example lens design, surgical manipulation, retained soft lens matter, reactions to chemicals on the intraocular lens surface (toxic lens syndrome), an immune reaction to lens protein (phacogenic uveitis), and infection. With the identification of *Propionibacterium acnes* in the vitreous of chronically inflamed eyes some authors[6] have come to wonder whether the organism may have a wider aetiological involvement. Infection may have been missed because it was never sought. Phacogenic uveitis is not thought to be infectious but it has been suggested that the *Propionibacterium* bacillus may act as an adjuvant to promote the host's immune response against his own lens protein.

A definitive plan for managing *Propionibacterium acnes* endophthalmitis has not yet been established. It seems appropriate to use an intravitreal injection of antibiotic (penicillin, clindamycin, or a cephalosporin) at the time of vitreous biopsy. Having cultured the organism one then has a variety of options. Some eyes have recovered good vision with a single intravitreal injection of antibiotic,[7] followed by topical and/or systemic treatment. Other eyes have needed complete removal of the capsular bag and contents and vitrectomy before the inflammation has subsided. It has been suggested that the chosen treatment approach should depend on the presenting visual acuity and the degree of intraocular inflammation,[8] reserving the extensive surgery for the more inflamed eyes. I hope that further advice will be forthcoming so that the rest of us may learn how to combat the infection with the least intervention thereby minimising the risk to already compromised eyes.

G VAFIDIS

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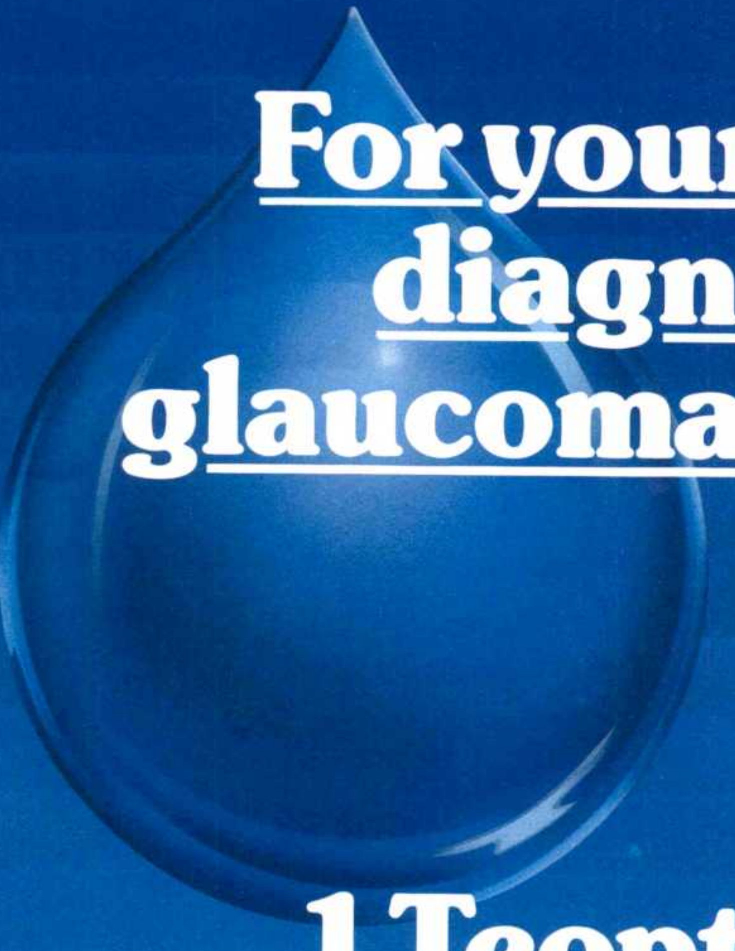

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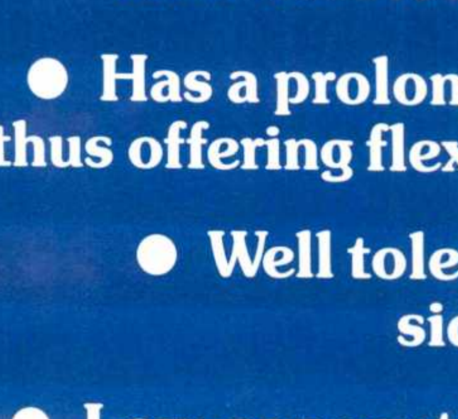

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British Journal of Ophthalmology, 1991, 75, 707–709

ORIGINAL ARTICLES

# Prandial presbyopia: the muffin man

Henry L Hudson, Vivian Rismondo, Alfredo A Sadun

## Abstract

**Transient blurring of near vision can be due to a variety of causes. We report the case of a 35-year-old man with a 10-year history of blurring of near vision that begins 30 to 45 seconds after he starts to eat and that lasts until 10 to 15 minutes after he stops eating. Magnetic resonance imaging and computed tomography of the brain and orbits did not reveal any abnormality, and stimulation of individual cranial nerves did not result in a loss of near vision. Retinoscopic refraction revealed the loss of 1·5 dioptres of accommodative power in each eye one minute after he began to eat. To the best of our knowledge such blurring of vision at near, immediately after initiating a meal, has not been previously reported. The neuroanatomy of the accommodation and of the gustatory pathways are discussed, as they may relate to this patient's visual complaint.**

Transient blurring of vision at near can be due to a variety of causes, including gaze evoked amaurosis, amaurosis fugax, transient obscurations of vision due to optic disc anomalies, dynamic accommodation insufficiency, migraine, and convergence insufficiency. Gaze evoked amaurosis is related usually to the presence of an orbital mass lesion. Amaurosis fugax is usually monocular, often associated with a vascular aetiology, and found in older patients. Migraine is typically associated with a visual phenomenon, such as a fortification scotoma. Acquired convergence insufficiency typically presents as diplopia at near and is often related to trauma or to a systemic illness such as diabetes. Dynamic accommodative insufficiency is found usually in younger patients, many of whom have no other abnormal physical findings.

We describe an adult male who presented with blurring vision at near that begins immediately after he begins eating. The neuroanatomy and physiology of the accommodative pathway is discussed as it may relate to this patient's ocular condition.

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A A Sadun

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H L Hudson.

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## Case report

A 35-year-old man was referred to the Doheny Eye Institute with a 10-year history of blurring of vision when eating. The patient stated that his vision begins to blur 30 to 45 seconds after he starts eating and remains blurry for 10 to 15 minutes after he ceases eating. Many foods provoke this, but particularly muffins, fruits, and sour foods. He has had no other ocular complaints, but he gave a history of head trauma in a fall from a catwalk in 1968. He reported a transient loss of consciousness at that time, but no examination was performed. He is on no medications, denies tobacco use, and reports drinking only a couple of alcoholic beverages at weekends. There is no history of toxic exposure, and the family history contains nothing relevant to his condition.

On physical examination the patient's visual acuity at distance was 20/20 in the right eye and 20/25-2 in the left eye. He had a near point of accommodation of 3 cm in the right eye and 4 cm in the left. He also had a near point of conversion of 4 cm. He could discern 14 of 14 American Optical test plates with each eye. The results of brightness sense testing, Amsler grid testing, tangent screen testing, and orbital examination were normal in each eye. The pupils were briskly reactive to light, and there was no afferent pupillary defect. The findings on slit-lamp biomicroscopy and dilated fundus examination were normal in each eye. Ocular motility examination revealed 10 dioptres of right esophoria at both distance and near. The patient also had minimal lid lag in the right eye. A general neurological examination, including the cranial nerves, gave results within normal limits.

Magnetic resonance imaging as well as computed tomography of the brain and orbits did not reveal any abnormalities. The patient's distance visual acuity was unchanged until he began to eat, at which time it decreased to 20/40 in each eye. However, he was refracted to 20/20 in each eye with the following correction: OD, +1·00+0·50×90, and OS, +0·75+1·00×90. More remarkable was his loss of vision at near, which went from Jaeger 1+ before eating to Jaeger 7 after eating. However, he could see Jaeger 1+ with the aid of a +3·00 lens over each eye. During a subsequent visit an attempt was made to elicit the loss of near vision by stimulation of individual cranial nerves. Following cranial nerve stimulation, baseline retinoscopy was performed, after which he was allowed to eat a large meal, during and after which his retinoscopic refraction at distance and near was monitored.

## Results

Stimulation of individual cranial nerves did not result in a loss of near vision (Table 1). However, one minute after beginning to eat the patient could read at near, without correction, only

*Table 1 Effect of cranial nerve stimulation on near vision*

| *Task** | *Cranial nerve stimulated* | *Effect* |
|---|---|---|
| Smell cloves | I | None† |
| Sustained upgaze | III | None |
| Sustained downgaze | III | None |
| Mastication | V | None |
| Taste salt on anterior ⅔ of tongue | VII | None |
| Taste grapefruit juice on posterior ⅓ of tongue | IX | None |
| Drink water | IX,X | None |

*All tasks were performed for 2 minutes.
†None=no change from baseline visual acuity at near, as assessed by Rosenbaum card

Jaeger 10 with the left eye and Jaeger 7 with the right eye. Fifteen minutes after finishing the meal he could read Jaeger 5 with the left eye and Jaeger 3 with the right. Thirty minutes after finishing the meal his visual acuity at near had returned to Jaeger 3 in the left eye and Jaeger 1+ in the right (baseline). These results were comparable to the changes in his accommodative power (Fig 1). Furthermore, the patient's visual acuity at distance was only slightly affected by eating, going from 20/20 OD and 20/25 OS before eating to 20/25 OD and 20/40 OS one minute after he began to eat. His retinoscopic refraction at distance was also only minimally affected by eating. No change in pupil size, reactivity to light, or reactivity to near was noted throughout the course of the examinations.

## Discussion

Blurring of vision at near immediately after initiating a meal has never to our knowledge been reported. Normally with accommodative effort caused by either a blurred retinal image or conscious visual fixation on a near object of regard a 'near synkinesis' is evoked, including increased accommodation of the lens,[1] convergence of the visual axes of the eyes,[2] and pupillary constriction.[3] A defect in any one of these elements could result in poor near visual acuity.

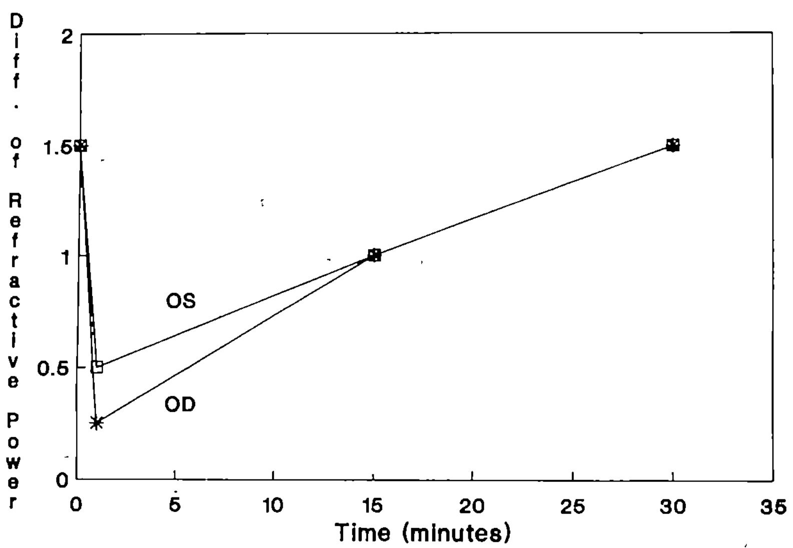

*Figure 1 Graph of accommodative power (vertical axis), defined as distance of retinoscopic refraction minus near retinoscopic refraction (in dioptres of sphere), versus time (horizontal axis). Note the almost total loss of accommodative power one minute after beginning to eat. The dioptres of cylinder, as well as the cylinder axis, remained unchanged throughout the examination (not shown)*

However, there was no evidence of convergence insufficiency or pupillary abnormalities in our patient, though retinoscopic refraction at near showed a loss of +1·5 dioptres of sphere in each eye one minute after he started to eat. This loss of accommodative power of the lens returned approximately 30 minutes after the meal was finished. Several explanations for a bilateral, transient loss of accommodative power of the lens related to eating could be considered.

The patient did give a history of head trauma, though patients who suffer posterior cortical injury typically have a permanent bilateral accommodative paresis.[1] Ocular trauma can also result in a loss of accommodative power, but this is ipsilateral to the injury, and therefore unlike that seen in our patient.

A synkinesis between the oculomotor nerve and another cranial nerve could be postulated as a cause of this patient's symptoms, but it would be extremely unlikely given the bilaterally symmetric nature of the accommodative loss. In addition, stimulation of individual cranial nerves did not evoke a loss of accommodative power in this patient. Moreover, one would expect stimulation of the ciliary fibres of the oculomotor nerve, via aberrant regeneration from another cranial nerve, to result in accommodative spasm, not paresis.

Review of the neuroanatomy of the accommodation pathway, as well as that for eating, swallowing, and digestion, may provide a clue to our patient's problem. The neural mechanisms of the accommodation pathway are not well understood, but it is likely that awareness of decreased distance of the object viewed evokes accommodative effort that originates in frontal centres; blurred retinal images are sensed in the prestriate cortex and are corrected via occipitotectal tracts.[2] A midbrain centre for accommodative vergence has not been shown anatomically but it is suggested on theoretical grounds.[3] However, the Edinger-Westphal nucleus in the rostral midbrain has been stereotactically mapped and may be divided functionally into a rostral part concerned with accommodation, a caudal part concerned with pupillary constriction, and an intermediate area that, when stimulated, results in both accommodation and pupillary constriction.[4] The parasympathetic fibres that innervate the ciliary body originate in the rostral part of the Edinger-Westphal nucleus and then course via the oculomotor nerve, the ciliary ganglion, and the short ciliary nerves. Stimulation of these fibres evokes constriction of the ciliary body, relaxation of the zonular fibres, and thickening of the lens, resulting in accommodation. This neuroanatomical pathway is far removed from the glossopharyngeal and vagal nuclei, which are located in the medulla and are involved in swallowing as well as in gastric secretion and motility.

It is intriguing, however, to speculate that the hypothalamus may provide the mediating pathway. The paraventricular hypothalamic nucleus (PVN) is believed to play an important part in the feeding mechanism. Feeding behaviour in satiated rats can be elicited by injecting a noradrenergic agonist into the PVN.[5] Furthermore, paraventricular nucleus activity can be modulated by electrical stimulation of the central stump of the vagus.[6] It is likely that the PVN sends efferent fibres to the dorsal motor nucleus of the vagus, from which the vagus nerve originates.[7] Afferents from the mouth, via cranial nerves IX and X, reach the paraventricular nucleus via the nucleus of the tractus solitarius.[8]

The PVN has been shown by autoradiographic tracing in cats to send efferent fibres to the Edinger-Westphal nucleus,[9] and in another study electrical stimulation of the diencephalon of sympathectomised cats and monkeys caused pupillary dilatation and abolished the light reflex.[10] This suggests the existence of a direct hypothalamic-mesencephalic pathway for inhibition of the Edinger-Westphal nucleus that may inhibit accommodation as well.

Eating (feeding) may thus result in stimulation of the PVN via vagal input to the nucleus of the tractus solitarius. Aberrant stimulation of the PVN may lead to firing of inhibitory fibres projecting to the rostral portion of the Edinger-Westphal nucleus. This could, at least theoretically, result in a loss of accommodation such as that seen in our patient. This aberrant pathway may have been present since birth, and may have become symptomatic only as the patient aged and his accommodative reserve diminished.

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# Posterior lens capsule abscess due to *Propionibacterium acnes* and *Staphylococcus epidermidis* following extracapsular cataract extraction

Ruth M Manners, Christopher R Canning

**Abstract**

**A case of posterior lens capsular abscess occurring many months after an extracapsular cataract extraction is presented. This was caused by a mixed infection involving *Propionibacterium acnes* and *Staphylococcus epidermidis*. The significance of *Staph epidermidis* after such a long postoperative period is uncertain, but the case shows features typical of secondary endophthalmitis due to *P acnes*, including a long delay in onset and a grumbling course not brought under control by medical treatment. It supports the theory that the nidus of infection is localised in the posterior lens capsule by showing development of a visible capsular abscess with associated vitreous involvement. The subsequent removal of the capsule and vitreous, despite leaving the intraocular lens in place, led to complete resolution of the inflammation. Both organisms have previously been found to be sequestered in the posterior lens capsule by histological and microbiological examination of excised capsular specimens. It is important to consider them as possible causative agents in the formation of a postoperative capsular abscess.**

There is an increasing awareness that the differential diagnosis of chronic, indolent, postoperative endophthalmitis, especially following extracapsular cataract extraction, should include the anaerobe *Propionibacterium acnes*. This is a ubiquitous organism found on skin and conjunctiva[1] and was generally previously dismissed as a contaminant. Propionibacteria are anaerobic, Gram-positive rods, and the organism may occur as a mixed infection as shown in the case presented here. It is highly sensitive to penicillin but less so to cephalosporins and resistant to gentamicin and vancomycin.[2] *P acnes* has also been reported as causing intralenticular abscess[3] and postoperative endophthalmitis following trabeculectomy and keratoplasty.

*Staphylococcus epidermidis* is an aerobic, Gram-positive organism of low virulence, commonly found in normal eyes and causally associated with postoperative endophthalmitis since 1964.[4] Generally the delay between surgery and postoperative infection is a matter of days and is thought to be due to antibiotics and steroids quelling the initial response. Latent periods of several months are rare.[5]

We report here a case of delayed postcataract extraction endophthalmitis due to a mixed infection of *P acnes* and *Staph epidermidis*. There are aspects of this case which suggest that the chronic infective source of the organisms in the eye was in the lens capsule.

In April 1989 a 79-year-old woman was admitted for left cataract extraction. Two years earlier a right extracapsular cataract extraction with posterior chamber lens implant had been performed, and her visual acuities then were 6/12 in the right eye and hand movement in the left with appropriate myopic correction.

An uneventful left extracapsular cataract extraction and posterior chamber intraocular lens insertion was performed under local anaesthesia. The procedure included a corneal section, needle can-opener capsulotomy, nucleus expression by external pressure, irrigation and aspiration with the Simcoe cannula, and insertion of an American Medical Optics posterior chamber, 22 dioptre intraocular lens, model PC57B, under viscoelastic substance which was subsequently aspirated. The section was closed with five 10/0 monofilament nylon sutures and the eye padded. The patient was discharged on the second postoperative day on chloramphenicol eyedrops 0·5% and dexamethasone eyedrops 0·1% four times a day.

The eye initially settled well following surgery, and five weeks postoperatively a visual acuity of 6/9 was achieved with appropriate correction. The eye appeared quiet and at this stage the posterior lens capsule was clear. All treatment was stopped.

Five months later the patient attended the casualty department complaining of pain and watering in the left eye for two days. On examination the left visual acuity was 6/12 with glasses. Conjunctival injection was present, with a quiet anterior chamber. The posterior lens capsule was noted to be slightly thickened. A diagnosis of conjunctivitis was made and treatment with chloramphenicol eyedrops 0·5% four times a day was started again.

On review one week later the eye was still painful and a moderately severe anterior uveitis was found. Therefore dexamethasone eyedrops 0·1% and cyclopentolate eyedrops 1·0% were started, and over the next month the inflammation gradually settled and topical treatment was eventually stopped. However, within one week the patient attended again with a severe recurrence of the inflammation. Posterior synechiae and corneal oedema were seen, and once again a thickened posterior lens capsule was noted. A conjunctival swab at this stage showed no growth. Intensive topical steroids and cycloplegics was restarted, and during the next month

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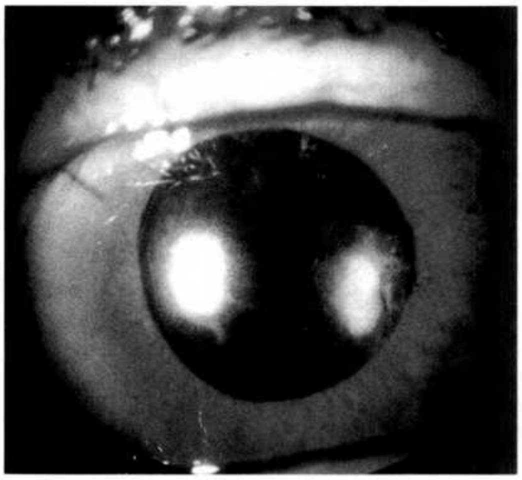

*Figure 1 Abscess of the posterior lens capsule extending posteriorly into the vitreous.*

the anterior chamber had settled sufficiently to allow a clear view of the lens capsule, which was seen to have developed a localised, whitish, dense opacity just inferotemporal to the visual axis. There was infiltrate extending back from this into the vitreous (Fig 1).

A diagnosis of endophthalmitis secondary to a posterior lens capsule abscess was made. Two days later a vitrectomy and capsulectomy were performed. An attempt was made to remove all abnormal looking capsule, leaving a peripheral annulus in which the lens was stable (Fig 2). During the procedure two specimens were taken: (1) capsular fluid, (2) vitreous. Intracameral antibiotics were not administered. A subconjunctival injection of cefuroxime 125 mg was given, and postoperative treatment was cefuroxime eyedrops 50 mg/ml two hourly, dexamethasone eyedrops 0·1% four times a day, and cyclopentolate eyedrops 1% four times a day. Oral flucloxacillin 250 mg and pivampicillin 500 mg four times a day and metronidazole 400 mg three times a day were given for seven days. All medication was tailed off over the next month. The eye has since remained quiet for six months and has a final visual acuity of 6/9.

### BACTERIOLOGICAL FINDINGS

Microscopy showed Gram-positive cocci and rods together with pus cells in the capsular fluid but no organisms in the vitreous.

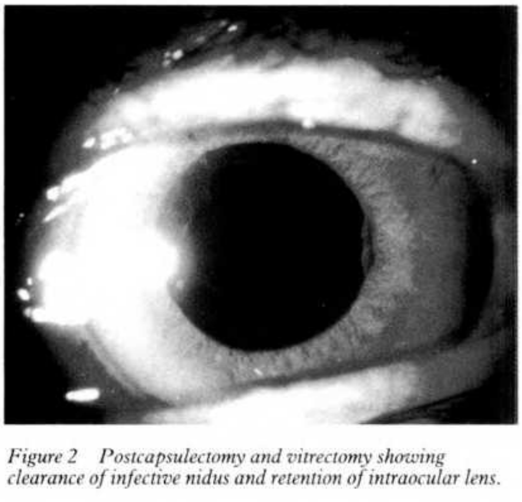

*Figure 2 Postcapsulectomy and vitrectomy showing clearance of infective nidus and retention of intraocular lens.*

Culture showed a mixed growth from both the capsular fluid and vitreous of *Propionibacterium acnes* and a single strain of coagulase negative *Staphylococcus* which showed colonial variation. The former was sensitive to penicillin and the latter to cloxacillin.

## Discussion

The many reported cases of postoperative *P acnes* endophthalmitis show a characteristic clinical course. The delay in onset is several months, and the inflammation then has a grumbling, insidious nature, often partially responding to antibiotics and steroids but recurring once topical treatment is stopped, as this case showed.[6] The significance of the *Staph epidermidis* is difficult to assess. It is known to cause postoperative endophthalmitis, but a delay of five months before onset of symptoms is atypical.

The vector by which the organism gains entry to the eye is thought to be the intraocular lens. Vafidis *et al*[7] showed that, when sterile intraocular lenses were placed on the conjunctival flap during cataract surgery, 26% became contaminated with organisms, mainly *Staph epidermidis*. They suggested that minimising contact of the lens implant with the eye before insertion would reduce the chances of intraocular infection. Griffiths *et al*[8] showed in vitro that *Staph epidermidis* can adhere to the plastic surface of the intraocular lens by producing a polysaccharide glycocalyx which acts like glue. Unfortunately this substance also seems to confer some resistance to antibiotics.

The intraocular lens used in this case was a one-piece, biconvex lens, posteriorly vaulted to an angle of 10° with no laser ridge. Thus it is assumed that the posterior capsule was apposed to the back surface of the lens with no intervening space. The presence of an IOL has been shown to increase the intensity and duration of *P acnes* infection in rabbit eyes, and possible explanations are that the IOL itself acts as a nidus for infection or that increased trauma during lens insertion may damage the blood-aqueous barrier, which will prolong the inflammatory response to intraocular bacteria.[9]

The case presented here showed clearly that the continuing infective site was the posterior lens capsule. Exudative material on the capsule and IOL occurring in the active stage of an indolent, granulomatous iridocyclitis has been previously reported by Meisler *et al*[10] Since the infection is thought to be associated with the lens capsule, it is more commonly found following extracapsular cataract extraction. Piest *et al*[11] examined capsule sacs that had been removed from cases of persistent, smouldering endophthalmitis and found pleomorphic bacilli in large numbers in the residual lens cortex and often in folds of capsule. In one case cultures were performed and *P acnes* grown. They thought that the capsule acted as a protective barrier preventing a full blown disseminated endophthalmitis, which was reported following a Nd-YAG laser capsulotomy. *Staph epidermidis* has also been reported to cause endophthalmitis following Nd-YAG capsulotomy in a previously quiet eye five months after extracapsular cataract extraction.[12] It was assumed that the low virulence micro-organisms had been sequestered in the capsular bag and released into the vitreous following laser treatment.

Ormerod *et al*[13] have found experimentally in rabbits that the local environment in the vitreous just posterior to the lens has an oxidation-reduction potential (Eh) and an oxygen pressure suitable for the growth of anaerobic organisms. They produced *P acnes* endophthalmitis which was self-limiting. Many factors may have suppressed these infections including the rise in Eh with inflammation above the limiting value for the anaerobic bacteria. Administration of 100% oxygen to the anterior chamber has thus been put forward as a treatment for this condition.

Clinically, when topical treatment fails to control the inflammation, further intervention is required. Zambrano *et al*[14] have suggested that less severe cases can be treated with intravitreal vancomycin (with or without topical and intravenous antibiotics) and have shown successful results. They suggest vancomycin as the initial choice since it is effective against *P acnes* and also coagulase negative staphylococci. Alternative antibiotics include methicillin and the cephalosporins. However, if the condition is initially severe or fails to respond to medical management, they recommend capsulectomy and pars plana vitrectomy together with intravitreal vancomycin. Our patient underwent such surgery without any antibiotics and the eye had improved dramatically within two days.

The intraocular lens alone does not appear to be the nidus of infection, since Meisler showed that whether or not the lens was removed in addition to the capsulectomy and vitrectomy made no difference to the successful outcome in their series of six cases. Driebe *et al*[15] found only one out of 57 cases of pseudophakic endophthalmitis in which the eye could not be sterilised while the intraocular lens was retained. Bacteria could have remained on the surface of the lens, but alterations in the local environment, such as loss of substrate cells and exposure to host defences by removal of the lens capsule, may have prevented regrowth. These theories are supported by the course in our patient who has retained her intraocular lens in a quiet eye for six months following surgery.

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# Anatomical factors influencing development of trichiasis and entropion in trachoma

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## Abstract

**There has been no published investigation into the reasons why some patients with severe trachomatous conjunctival scarring develop entropion and trichiasis while others do not. In a population of leprosy patients with severe trachomatous conjunctival scarring the authors found that lagophthalmos correlated with the absence of trichiasis and entropion. We suggest that orbicularis oculi muscle function, as well as other anatomical variations among individuals, may contribute to the development of trachomatous entropion and trichiasis in patients with conjunctival scarring.**

Trachoma remains the leading cause of preventable blindness worldwide.[1] Blindness is secondary to corneal scarring caused by chronic entropion and trichiasis, which are associated with scarring of the superior tarsal conjunctiva after chronic infection with *Chlamydia trachomatis*. However, not everyone who is infected with the causative agent becomes blind. Some investigators have suggested that trachoma may be an immunopathological disease, and that repeated reinfection with the causative organism, perhaps exacerbated by superinfection with other organisms, is necessary to cause severe conjunctival scarring.[2 3]

Another issue in the development of trachoma blindness is why only some of the patients who have severe scarring of the conjunctiva develop entropion and trichiasis. The magnitude and cause of this variability have not been established. As part of a separate study on cellular response and conjunctival scarring we examined leprosy patients in a trachoma endemic region of Ethiopia. We noticed that there was less trichiasis/entropion among leprosy patients with lagophthalmos than among those who had normal orbicularis function. Leprosy patients often have weakness of the orbicularis oculi muscle, and we considered whether this factor might influence the development of entropion. Thus we analysed relevant data collected to examine this hypothesis.

## Materials and methods

Leprosy patients from the Sheshamane area of South Shoa province in Ethiopia, where trachoma is hyperendemic, were examined from February to May 1990. One examiner (SL) conducted all the examinations and recorded the following data for each patient: age, sex, conjunctival scarring, trichiasis/entropion, and presence of lagophthalmos. Conjunctival scarring and trichiasis/entropion were graded according to the WHO (non-simplified) grading scheme.[1] Eyes with severe (grade 3) conjunctival scarring were used for analytic purposes.

Data were entered on a computer and analysed in a 2×2 table by Fisher's exact test and multiple logistic regression analysis. Since lagophthalmos may be unilateral the data were analysed by eye rather than by individual.

## Results

Thirty seven patients (53 eyes) had severe conjunctival scarring. The ages of the patients ranged from 33 to 75 years, median 50. None of these patients had leprosy related loss of eyelashes. One patient with trichiasis/entropion due to a leprosy nodule on the lid was excluded from the analysis. We chose the eye with severe scarring in cases of monocular scarring ($n=19$) and the left eye was chosen in cases of binocular severe scarring ($n=18$).

Of the 37 patients with severe conjunctival scarring 16 had lagophthalmos. Only one of these patients had coexisting grade 3 trichiasis/entropion. In contrast, 21 patients with severe scarring had no lagophthalmos, and nine of these had coexisting grade 3 trichiasis/entropion (Table 1). Logistic regression analysis revealed that neither age nor sex confounded the association between lagophthalmos and grade 3 trichiasis/entropion. The average age of patients with trichiasis/entropion was the same (51 years) as that of patients without trichiasis/entropion.

## Discussion

Since entropion and trichiasis are frequently the cause of the blindness that results from trachoma it is relevant to ask why some patients with conjunctival scarring develop this while others do not. Lagophthalmos appears to be a factor protecting some leprosy patients with trachomatous conjunctival scarring from developing entropion. Obviously in the non-leprosy population lagophthalmos itself is not common enough to be proposed as a significant protective factor.

*Table 1 Presence of trichiasis/entropion among patients with severe conjunctival scarring*

| | Number of patients with trichiasis/entropion | | |
|---|---|---|---|
| | *Grade 0–1* | *Grade 2* | *Grade 3* |
| No lagophthalmos | 9 | 3 | 9 |
| Lagophthalmos | 13 | 2 | 1 |

Correlation: Grade 3 (severe) trichiasis/entropion. odds ratio=0·09 (95% confidence interval 0·01, 0·89); Fisher's exact one-tailed p value=0·01. Grades 2+3 (moderate+severe) trichiasis/entropion odds ratio=0·17 (95% confidence interval 0·03, 0·96), Fisher's exact one-tailed p value=0·02.

However our findings suggest that anatomical variations among individuals, specifically orbicularis oculi strength, may influence the development of entropion and trichiasis in the face of severe conjunctival cicatrisation. Deep insertions of the pretarsal orbicularis within the orbital rim allow a posterior pull on the eyelids to maintain apposition to the globe. The relative strength of marginal fibres of the orbicularis in comparison with the rest of the pretarsal or preseptal orbicularis may influence the likelihood of the tarsus rotating inward. The development of involutional entropion of the lower lid is thought to be related to such anatomical factors.[4] Some of these same factors may play a role in development of trichiasis/entropion once cicatrisation of the conjunctiva has occurred.

These data were not collected for the purpose of assessing the correlation between lagophthalmos and trichiasis/entropion and there are some limitations to our using them thus. Our findings are limited by the use of the WHO grading system for trichiasis/entropion, which is a better measure of trichiasis than of the entropion. To examine the role of an individual's lid anatomy in the development of entropion it would be preferable to grade lids according to a system which separates the degree of entropion and lid deformity from the number or position of inturning lashes. Such a system was suggested by Sarkies in 1965.[5] The presence of lagophthalmos is a gross measure of orbicularis strength, and obviously lagophthalmos is not the factor protecting patients with severe scarring in the on-leprosy population from developing entropion. However, orbicularis strength may be an important risk factor, as may other variations in individual lid anatomy. Further investigations would help clarify the pathogenesis of blinding trachoma and prove useful in enhancing the identification of patients at highest risk of blindness from this disease.

This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) Dr Lewallen was supported by Christoffel Blindenmission The authors acknowledge the support of the Ministry of Health, Addis Ababa, Ethiopia

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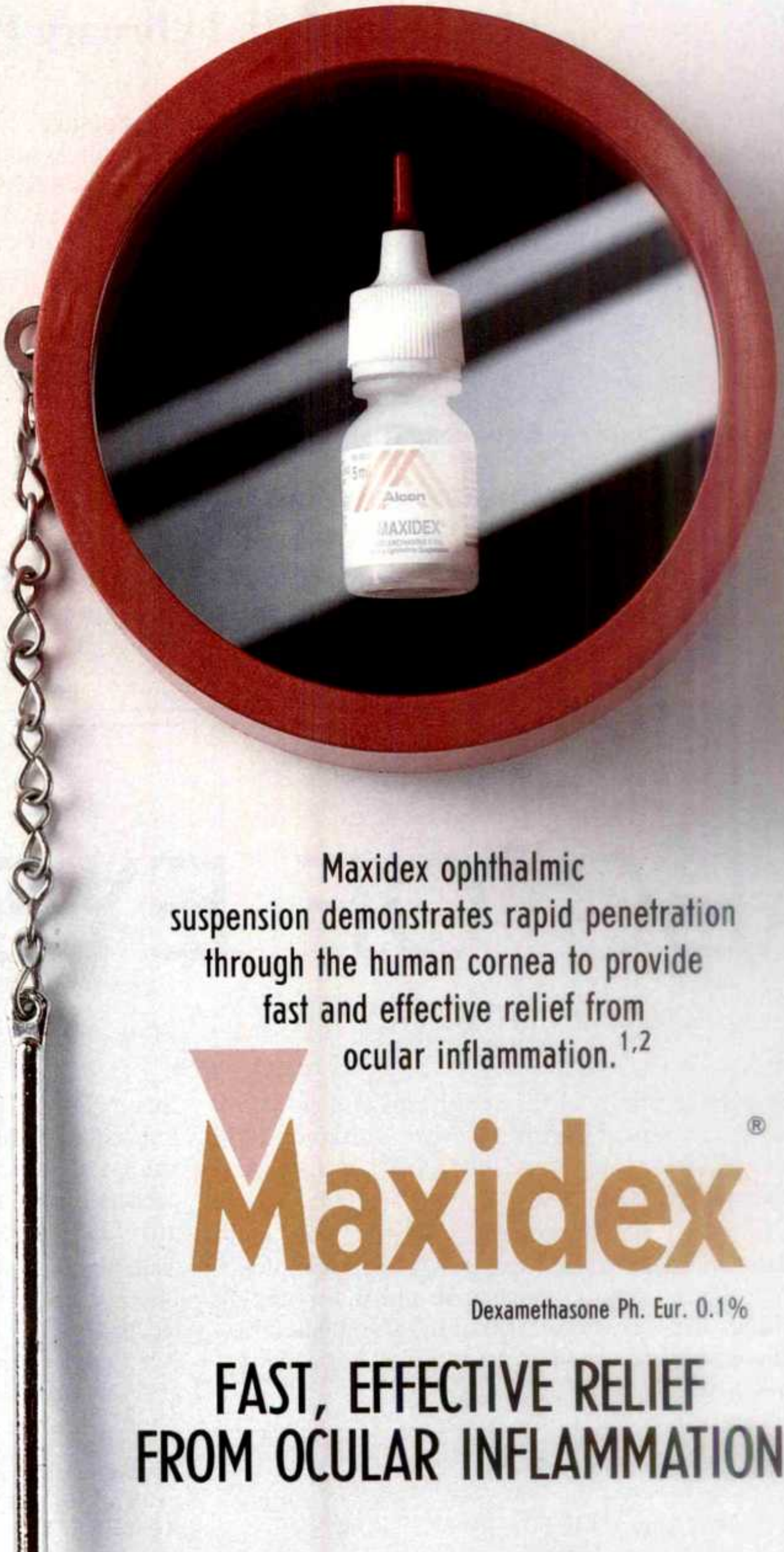

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# Treatment of juxtapapillary melanomas

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## Abstract

**Thirty nine patients suffering from juxtapapillary choroidal melanoma were treated with Ru-106/Rh-106 β-ray plaques. The tumoricidal dose was 100 Gy at the apex of the tumour within 7–14 days. Additional photocoagulation was performed in 12 eyes. The irradiated eyes of three patients had to be enucleated, seven patients died, five of them (12·8%) from metastases. Thirty two (82%) patients are alive and 29 (74%) have a seeing eye. From the whole series 20 (51%) developed flat scars and 11 (29%) patients retained a visual acuity of 0·5–1·0. Radiogenic late complications with damage to the optic nerve and macula were the main causes of visual deterioration.**

Naevi and malignant choroidal melanomas are mostly located at the posterior part of the uvea, possibly due to the fact that ciliary nerves are more concentrated in this region than in other parts of the fundus.[1]

Juxtapapillary growth of a malignant melanoma is the most challenging for any conservative therapeutic procedure. On the one hand the malignant tissue must be completely destroyed and on the other hand the macula and optic nerve located closest to the tumour margin should be preserved from destructive side effects of the ionising radiation. The optic nerve, vortex veins, and the insertion of the inferior oblique muscle sometimes hamper the proper suturing of radioactive plaques which have to cover the tumour margin.

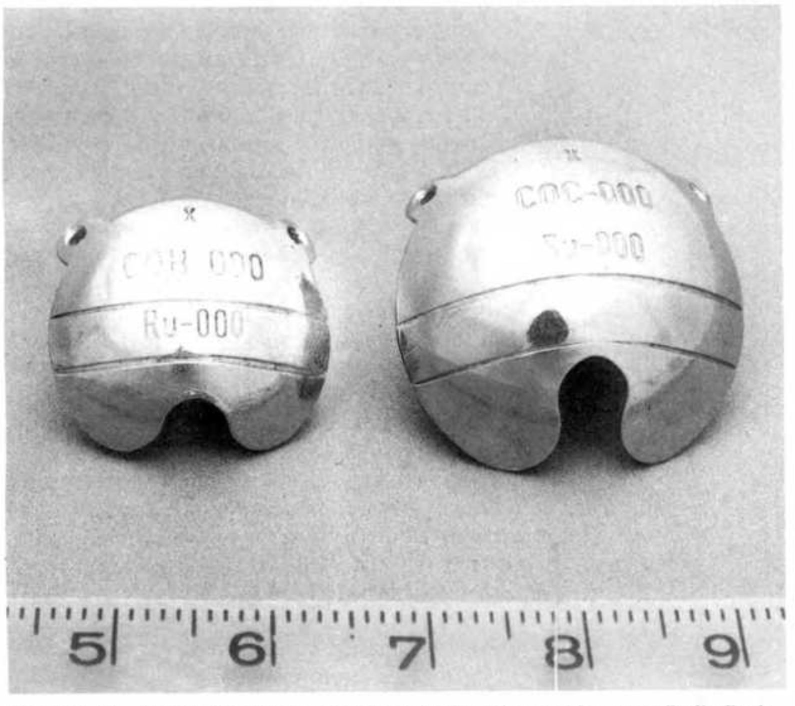

*Figure 1 Ru-106/Rh-106 plaques with a notch for the optic nerve (Isocomerz Berlin-Buch, Germany).*

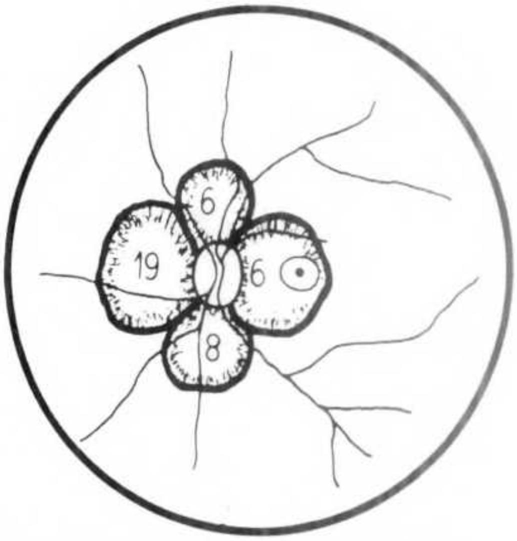

*Figure 2 Location of the 39 juxtapapillary choroidal melanomas.*

The aim of this paper is to present our clinical experience of the management of these juxtapapillary choroidal melanomas.

## Patients and method

Thirty nine patients suffering from juxtapapillary choroidal melanomas were treated between 1964 and 1986. Each melanoma approached the optic disc or was growing less than half a disc diameter (DD) distant from it. During the same period 387 patients were treated with Ru-106/Rh-106 plaques, which means that roughly 10% of all these cases were tumours growing close to the optic disc. Diagnosis was confirmed by ophthalmoscopy and ultrasonography. Treatment was performed with Ru-106/Rh-106 plaques as described in previous papers.[2]

In most of these tumours we used plaques which have a sector cut out to accommodate the optic nerve (Fig 1). Under local or sometimes general anaesthesia the conjunctiva and Tenon's capsule were incised and, if necessary, muscles were detached so that the plaque could be placed on the sclera as close as possible to the tumour base, which was carefully localised by transillumination or diathermy. The therapeutic dose was calculated to deliver 100 Gy at the apex of the tumour within seven to 14 days.

In 12 eyes additional photocoagulation with xenon was performed after brachytherapy in those cases in which the central margin of the tumour showed insufficient regression. A dense line of heavy coagulation burns was arranged horseshoe-like around the central rim of the tumour.

Tumour regression was recorded on follow-up examinations by fundus photography, ultra-

*Table 1 Regression after treatment (median follow-up period 4·6 years)*

| *Tumour size before treatment* | | *Flat scar* | *Tumour height <1 mm* | *Tumour height 1–2 mm* | *No regression* | *Further tumour growth* |
|---|---|---|---|---|---|---|
| *Small* (less than 3 mm in height or 10 mm in diameter) | 11 | 8 | 3 | 0 | 0 | 0 |
| *Medium* (less than 5 mm in height or 15 mm in diameter) | 17 | 10 | 2 | 3 | 1 | 1 |
| *Large* (Larger than 5 mm in height or 15 mm in diameter) | 11 | 2 | 3 | 4 | 1 | 1 |
| Total | 39 (100%) | 20 (51%) | 8 (21%) | 7 (18%) | 2 (5%) | 2 (5%) |

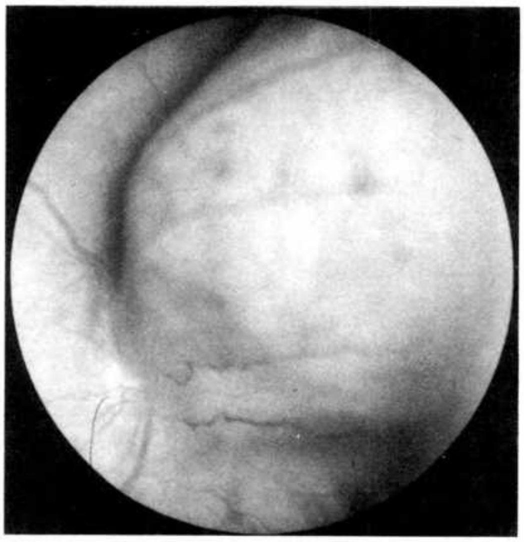

*Figure 3A Female patient aged 53 years. Choroidal melanoma of the right eye growing nasally adjacent to the disc, height 7·8 mm.*

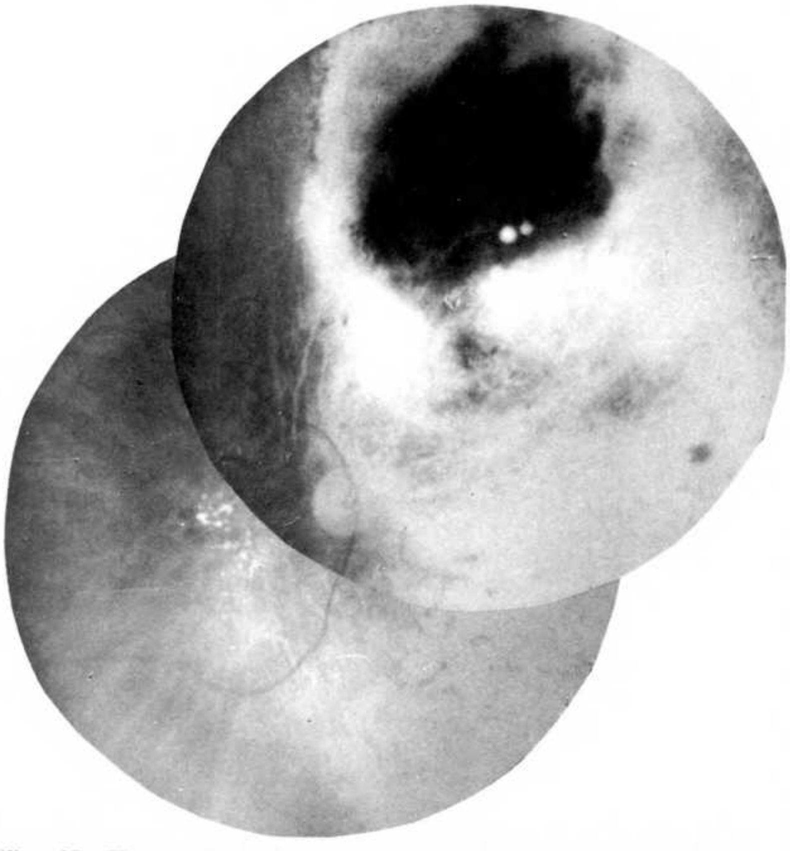

*Figure 3B Five years after brachytherapy with Ru-106/Rh-106 plaque (240 Gy in 5 mm, 1000 Gy at the scleral surface) and xenon photocoagulation at the temporal rim. VA=0·04.*

*Table 2 Juxtapapillary choroidal melanoma (n=39)*

| | *Visual acuity* | | |
|---|---|---|---|
| | *Before treatment* | *One year after treatment* | *Final examination (median follow-up period 4·6 years)* |
| 1·0–0·5 | 25 | 18 | 11 |
| 0·4–0·2 | 9 | 5 | 8 |
| 0·15–0·02 | 5 | 13 | 16 |
| <0·02 | – | 3 | 4 |

*Table 3 Juxtapapillary choroidal melanoma (n=39) seven died – five from metastases*

| *Size* | *Follow-up period* | *Regression* | *Cause of death* |
|---|---|---|---|
| 1. medium | 6 years | flat scar | metastases (autopsy) |
| 2. medium | 8 years | tumour remnants (2 mm) | arteriosclerosis |
| 3. medium | 3·2 years | flat scar | metastases (autopsy) |
| 4. medium | 1·6 years | flat scar | metastases |
| 5. medium | 3·6 years | tumour remnants (1 mm) | metastases |
| 6. large | 6 years | tumour remnants (2 mm) | metastases (autopsy) |
| 7. large | 6 years | flat scar | rectal carcinoma |

sonography and fluorescein angiography. The median follow-up period was 4·6 years. The tumours in 19 patients were controlled for more than 5 years.

## Results

The average age of our patients was 50 years, the youngest was 23 and the oldest 68 years. The sex distribution was 23 male and 16 female patients. The right eye was involved in 21 cases and the left eye in 18 cases. The melanoma was located nasal to the disc in 19, below in eight, above in six and temporal, including the macular area, in six cases (Fig 2).

The pretreatment tumour sizes were as follows: 11 small tumours (less than 3 mm in height or less than 10 mm in diameter), 17 medium sized tumours (more than 3 mm but less than 5 mm in height or more than 10 mm but less than 15 mm in diameter) and 11 large tumours (larger than 5 mm in height or larger than 15 mm in diameter).

Out of the 39 patients, seven died during the follow-up period, five from proved metastases (13%). Three eyes had to be enucleated because of insufficient tumour regression.

Tumour regression after irradiation in relation to the pretreatment tumour sizes is shown in Table 1.

Visual acuity before, 1 year after irradiation, and at final examination is shown in Table 2. Before treatment 25 patients (64%) had a visual acuity between 0·5 and 1·0. After brachytherapy, 11 (28%) still had this good visual acuity at the last follow-up examination.

The majority of radiogenic complications included macular degeneration, papillitis and atrophy of the optic nerve which led to deterioration of the visual function. Macular destruction was found in 16, atrophy of the optic disc in 10, papillitis in six, radiogenic retinopathy in five, vitreous haemorrhage in three eyes and secondary glaucoma in one eye.

Three eyes (two with medium sized and one with a large melanoma) had to be enucleated

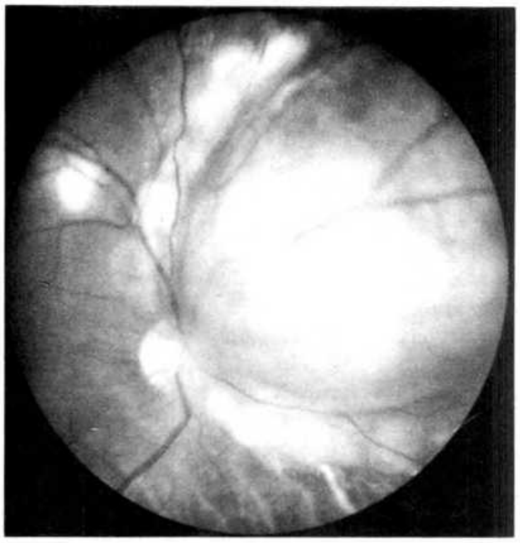

*Figure 4A Male patient aged 44 years. Choroidal melanoma of the right eye growing nasally adjacent to the disc, height 4 mm. Brachytherapy with Ru-106/Rh-106 plaque (240 Gy in 5 mm, 1000 Gy at the scleral surface) and xenon photocoagulation at the temporal rim. One result of coagulation was accidentally incorrectly situated.*

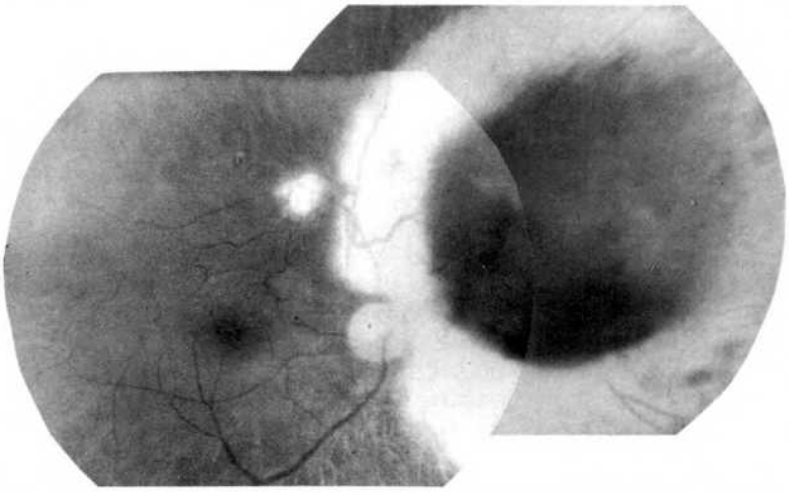

*Figure 4B Six years after treatment. Atrophic scar with a pigmented slightly elevated mass in its centre (3·4 mm by ultrasonography high reflectivity). VA=0·1.*

because of inadequate tumour regression at 2 months, 5 years, and 9 years after treatment. Histological examination showed spindle cell A melanoma in all cases. Five patients died from metastases as shown in Table 3. However three of these sustained an excellent tumour regression to a flat scar after treatment.

## Discussion

The therapeutic outcome after brachytherapy using Ru-106/Rh-106 plaques in patients suffering from choroidal melanoma depends on the pretreatment size and the location of the tumour. In cases of juxtapapillary melanomas in particular we have to expect a worse prognosis regarding visual acuity and tumour regression in comparison with those tumours growing at the equator. The reasons are the radiosensitivity of the optic nerve, the vicinity of the fovea which sometimes has to be included in the irradiation area, and the impossibility of reaching all tumour cells with a plaque—even using those with a recess for the optic nerve. In such a situation additional light or laser coagulation can be used after radiotherapy (as we did in 12 eyes) to destroy the central tumour margin and to interrupt the feeding choroidal vessels in the vicinity of the optic disc.

There were five deaths (13%) from metastases in this series. This is similar to the 11% metastasis rate after 5 years reported in our statistical analysis, including all locations of choroidal melanomas.[2]

Proximity of choroidal melanomas to the optic nerve and to the fovea is always a risk factor for visual loss after any kind of radiotherapy.[3] The severity and extent of post-radiation retinopathy after brachytherapy with Ru-106/Rh-106 plaques is less than after cobalt-60[4] because of the higher volume dose of the latter.

Nevertheless using β rays from Ru-106/Rh-106, with the limited penetration depth into tissue, is an effective method for destruction of tumours even those close to the optic disc (Figs 3 and 4). It seems to be a recommendable alternative to enucleation, proton beam irradiation,[5] iodine-125 plaques,[6] or local tumour resection.[7,8]

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British Journal of Ophthalmology, 1991, 75, 718–721

# Phototherapy of posterior uveal melanomas

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## Abstract

**The results of phototherapy on a small series of 19 patients with uveal melanomas are presented. Laser radiation at a wavelength of 620 to 630 nm was used in conjunction with a 5 to 7·5 mg/kg dose of haematoporphyrin derivative administered 24 hours before treatment, with total doses/treatment averaging 960 J/cm$^2$. Eleven patients received two treatments, and one received a third. The longest duration of tumour control to 30 September 1990 was 31 months. Of the 19 patients treated six had complete regression of the tumour, while another five had minor to significant regression. A strong correlation between degree of regression and degree of tumour pigmentation was found, the lighter tumours responding much better than darker tumours. There were also strong indications that if a tumour did not respond to the initial phototherapy it was very unlikely that subsequent phototherapy would provide any further benefit.**

For over a hundred years enucleation has been the traditional method of treatment for posterior uveal melanomas, particularly for large tumours. However, its singular lack of success in increasing life expectancy[1] has led to alternative methods of treatment, with radiotherapy being the most effective and widely used.[2-4] Since recent reports have shown that enucleation and radiotherapy have essentially equivalent survival rates,[5-7] new forms of therapy such as phototherapy need to be evaluated.

Phototherapy (PT) has been shown to destroy implanted melanomas and retinoblastomas in animals, with few adverse effects.[8,9] The operation of PT is based on the fact that malignant tissue selectively retains a photosensitiser such as haematoporphyrin derivative (HpD). If the sensitiser is subsequently activated with light of an appropriate wavelength, it releases high-energy radicals which cause tumour cell destruction.[10] Although the use of light-sensitive substances in the treatment of disease was described as early as 4000 BC,[11] it was first used successfully to treat basal cell carcinomas in 1905.[12] Since then it has been used to treat many different forms of cancer with varying degrees of success and with minimal side effects.[13,14]

The few reports of phototherapy for posterior uveal melanomas in humans have been encouraging, despite the small numbers, short follow-up, and varied response. In one series seven posterior uveal melanomas were treated with one complete response in an amelanotic melanoma of 9·4 mm height at the posterior pole followed up for four years, with varied to zero response in the others.[15] In another report, of 23 patients, the greatest tumour reduction occurred in melanomas of less than 1000 $cm^3$ volume, with no adverse systemic side effects from HpD.[16] Marked necrosis extending to the base of the melanoma has been reported in enucleated specimens following PT.[17]

HpD has been the photosensitiser most widely used. It binds tightly to serum proteins, including lipoprotein carriers, and there is a linear relationship between cell volume and uptake.[18] Animal experiments have shown that it localises in vascular structures of the eye (choroid, iris, retina) within 48 hours of intravenous administration, with lower concentrations in the sclera, and with none located within the cornea and lens.[19] In experimental tumours it is concentrated in the vascular stroma (macrophages, mast cells, and possibly fibroblasts), with a lower concentration in the cells, and the earliest histological change following PT is bleeding of tumour cells adjacent to the microvasculature.[20] The actual mechanism by which tumour cells are destroyed is not clear, though ischaemia,[21,22] destruction of cell membrane functions, intracellular enzyme inhibition, and DNA damage probably initiated by singlet oxygen production[23] and other radicals have been reported.[24] Ocular toxicity studies have shown that its acute effects are confined to the treated area, and the chronic changes are non-progressive.[19] Its major side effect is skin photosensitisation for up to 80 days following administration.

This report describes the effects of PT on a small series of choroidal melanomas.

## Materials and methods

Under a management protocol approved by the Research (Advisory and Ethics) Committee at Prince Henry's Hospital, Melbourne, and with informed consent, 19 patients with posterior uveal melanomas diagnosed by ophthalmological examination, fluorescein angiography, and ultrasonography were treated with PT after growth had been demonstrated by an increase in volume in consecutive measurements (17 patients), or at the patient's request (patients 76 and 80). Tumour size was assessed by volume in accordance with previously reported methods by a 'blind' observer.[25,26] Location of the anterior margin of the tumour was graded as posterior to the equator, equatorial, or anterior to the equator, and tumour pigmentation was graded as deeply, moderately, or lightly pigmented as determined by indirect ophthalmoscopy and colour photographs. All patients were examined by an oncologist and received whole body CT scans. A full blood examination and renal and liver function tests were performed prior to treatment. Exclusion criteria were the presence of clinical porphyria, metastases, pregnancy, allergic reactions to HpD, and tumours more than 10 mm in height.

Patients were treated with a pulse-injected

*Table 1 Degree of pigmentation, position, pretreatment height and volume, PT dose, degree of regression, and other details for 19 patients treated with PT*

| Patient no. | Colour pigment | Position of of tumour | Pretreatment size |  | First treatment (months) |  |  | Second treatment (months) |  |  | Third treatment (months) |  |  | Degree of regression overall | Enucleated eye cell-type |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | Height mm | Volume mm$^3$ | Total dose $J/cm^2$ | To 30 Sept 90 or to 2nd treatment | Deg reg | Total dose $J/cm^2$ | To 30 Sept 90 or to 3rd treatment | Deg reg | Total dose $J/cm^2$ | To 30 Sept 90 or since 3rd treatment | Deg reg |  |  |
| 2 | Dark | Post | 4·1 | 111 | 1490 | 7·8 | NR | 1150 | 12·9 | NR |  |  |  | NR | Spindle cell |
| 22 | Dark | Post | 6·6 | 255 | 1300 | 13·3 | NR | 1410 | 12·6 | NR | 1300 | 6·5 | NR | NR |  |
| 58 | Dark | Post | 3·3 | 175 | 1000 | 23·6 | NR |  |  |  |  |  |  | NR | Spindle cell |
| 1 | Dark | Post | 3·3 | 129 | 130 | 9·2 | NR | 2200 | 31·3 | NR |  |  |  | NR |  |
| 64 | Dark | Equ | 4·4 | 167 | 920 | 9·5 | MR | 674 | 2·4 | NR |  |  |  | NR |  |
| 125 | Dark | Post | 2·0 | 29 | 1190 | 5·4 | SR |  |  |  |  |  |  | SR |  |
| 9 | Moderate | Post | 2·6 | 76 | 980 | 21·4 | NR | 720 | 13·7 | NR |  |  |  | NR | Spindle cell |
| 11 | Moderate | Post | 5·3 | 100 | 1100 | 5·1 | NR | 1280 | 22·1 | NR |  |  |  | NR | Epithelioid |
| 112 | Moderate | Equ | 5·2 | 193 | 920 | 9·0 | NR | 710 | 2·8 | NR |  |  |  | NR |  |
| 7* | Moderate | Post | 4·4 | 211 | 780 | 7·8 | NR | 1180 | 27·0 | MR |  |  |  | MR |  |
| 16 | Moderate | Post | 5·5 | 649 | 260 | 6·2 | NR | 770 | 31·3 | SR |  |  |  | SR |  |
| 116 | Moderate | Ant | 4·0 | 55 | 595 | 6·7 | MR |  |  |  |  |  |  | SR |  |
| 25 | Moderate | Post | 4·7 | 151 | 1120 | 17·[illegible] | SR |  |  |  |  |  |  | SR |  |
| 76 | Moderate | Post | 1·2 | 13 | 320 | 9·0 | SR | 740 | 16·4 | CR |  |  |  | CR |  |
| 72 | Moderate | Post | 3·9 | 93 | 790 | 18·4 | SR | 992 | 6·0 | CR |  |  |  | CR |  |
| 77 | Moderate | Post | 4·7 | 82 | 1140 | 11·3 | [illegible] |  |  |  |  |  |  | CR |  |
| 8 | Moderate | Post | 2·6 | 111 | 960 | 27·2 | CR |  |  |  |  |  |  | CR |  |
| 80 | Light | Equ | 5·0 | 145 | 960 | 23·5 | CR |  |  |  |  |  |  | CR |  |
| 132 | Light | Equ | 8·9 | NA | 760 | 1·9 | CR |  |  |  |  |  |  | CR |  |

NR=no regression. MR=minor regression. SR=significant regression. CR=complete regression. Deg reg=degree of regression. *Patient dead.

intravenous infusion of HpD obtained from the Queen Elizabeth Hospital, South Australia, dosage 5–7·5 mg/kg body mass. For all patients, monochromatic light of 620-630 nm wavelength and 1000 µm beam width from a coherent argon/dye laser was delivered through the pupil on to the surface of the melanoma via a Rodenstock panfunduscope lens and/or Goldman three-mirror lens, in two sessions 24 and 48 hours after administration of HpD. For three patients additional light was delivered transclerally by a 1 mm diameter fibreoptic bundle applied to the tumour base. The total dose in $J/cm^2$ received by each tumour was calculated from its basal surface area measurement, or best estimate, and is listed in Table 1.

Eight patients with posterior uveal melanomas which showed either zero or insufficient response received a second treatment (mean 10 months, ranging from 5 to 21 months following the initial treatment). One patient received three treatments. All patients received systemic prednisolone 10 mg/day, topical atropine 1%, and prednisolone 1% for four weeks following treatment.

All patients wore protective clothing,

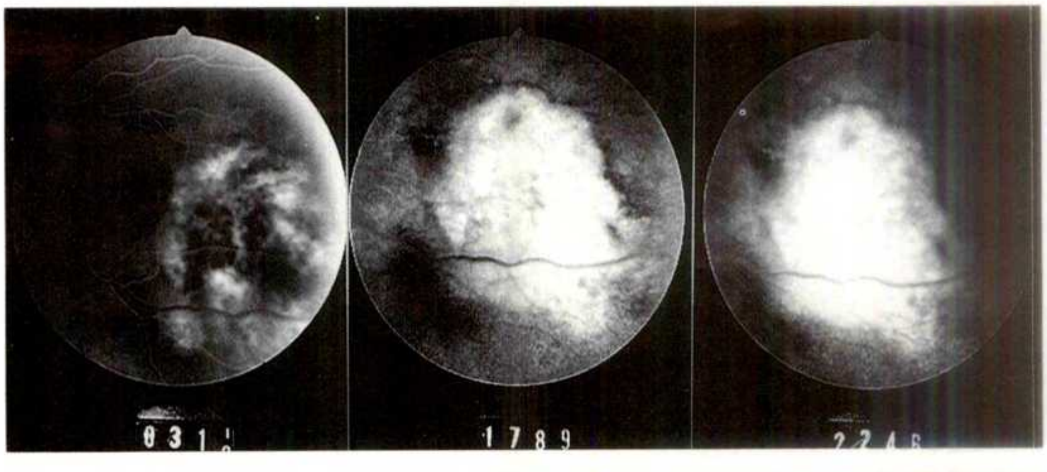

*Figure 1 Fluorescein angiogram prior to PT (patient 8): early, middle, late frames.*

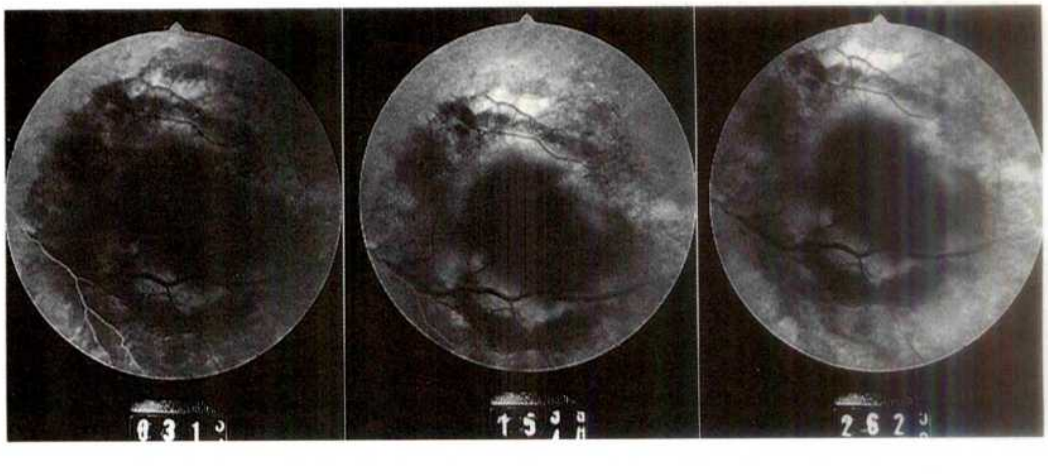

*Figure 2 Fluorescein angiogram following PT (patient 8): early, middle, late frames.*

ultraviolet-block skin creams, and avoided direct sunlight for a minimum period of 45 days following treatment. They were regularly reviewed, with measurement of visual acuity with and without pinhole, slit-lamp biomicroscopy, clinical photography, and serial measurement of the melanoma volume.

## Results

Tumour response to treatment was classified into four grades:

(1) Complete regression (CR): no evidence of tumour macroscopically to end of the current follow-up period (30 September 1990).

(2) Significant regression (SR): more than 50% reduction of original tumour size to the end of the current follow-up period.

(3) Minor regression (MR): up to 50% reduction of original tumour size to the end of the current follow-up period.

(4) No regression (NR): no change or continued growth after treatment.

Apart from one patient who died, none was lost to follow-up. The results are summarised in Table 1. To illustrate the relation between the degree of pigmentation and the level of regression the table is sorted in order of pigmentation (from dark to light) as the primary sort condition, with regression (from none to complete) as a secondary criterion.

After one session of PT a complete response was seen in four of the 19 patients (21%), while a further six showed a partial response (31%). After a second application of PT the number of cases showing a complete response increased to six (31%), while the number showing a partial response remained at six (31%). As of 30 September 1991 there was no sustained regression or continued growth of tumour in eight patients (42%).

The longest duration of tumour control was 31 months to 30 September 1990. The average PT dose per treatment was 960 $J/cm^2$ for the 31 treatments given. One patient (patient 7) who had MR following treatment died as a result of hepatic metastases three years after diagnosis and two years after PT.

The posterior uveal melanomas which regressed following PT exhibited fluorescein angiographic evidence of tumour and choroidal vascular occlusion and elimination of fluorescein leakage (Figs 1, 2).

Of the eight patients showing NR, six received two treatments, and one received three. No patient experienced any adverse side effect as a result of multiple treatments. For those tumours that showed either NR or MR as a result of PT, neither a second nor third treatment produced further improvement except in one patient (patient 16). We now believe that tumour regression occurred in this patient following the first treatment but was masked by a large overlying serous retinal detachment. Two patients with an initial CR of melanomas at the posterior pole received a second treatment resulting in CR for recurrences arising from the tumour edge, and extending into the macular area which had been deliberately avoided in the initial treatment. Four eyes which showed NR, of which three had second treatments, were enucleated. Histopathology, including transmission electron microscopy, showed active tumour cell growth in all eyes with extrascleral extension in one (patient 9).

*Table 2 Spearman rank correlation analysis parameters: relationship of degrees of regression of choroidal melanomas with pre-PT treatment height, volume, initial dose, cumulative dose, and degree of pigmentation*

| *Parameter (correlated with four levels of degree of regression)* | *Corr coeff* | *Significance* |
|---|---|---|
| Height (1 mm inc.) | −0·03 | 0·91 (NS) |
| Volume (100 $mm^3$ inc.) | −0·18 | 0·48 (NS) |
| Initial PT dose (500 $J/cm^2$ inc.) | −0·07 | 0·79 (NS) |
| Cumulative PT dose (500 $J/cm^2$ inc.) | −0·59 | 0·006 (S) |
| Degree of pigmentation (3 levels) | 0·71 | 0·0005 (S) |

inc. = increment NS = not significant at 5% level. S = significant

Table 2 lists Spearman's rank correlation coefficients and significance levels for the relationship between degree of regression with tumour height, volume, initial and cumulative PT doses, and degree of pigmentation. There was no significant correlation with height, volume, or initial PT dose. Cumulative dose showed a strong negative correlation with degree of regression, which implies that if a tumour does not respond to initial PT it probably will not respond to further treatment. Very strong correlation was found between degree of regression and degree of pigmentation; the less the pigmentation, the greater the degree of regression.

## Discussion

Despite the small size of this series the short-term results following PT were encouraging. The lack of correlation between tumour response and its physical attributes, apart from the degree of pigmentation, highlights the unpredictability of the PT response owing to multiple factors including photosensitiser type, dosimetry and tissue uptake, and the total dose of light energy. Although HpD is the most commonly used sensitiser for PT, it is not ideal. It maximally absorbs light at 390 nm wavelength; but because this wavelength has poor tissue penetration, the minor absorption peak at 630 nm wavelength, which penetrates tissues more effectively, but requires relatively more energy, is generally used. The poor response of the six deeply pigmented melanomas suggests that they may have received a lower than calculated total light energy dose. Transcleral delivery of light energy in addition to transpupillary delivery may overcome the problems of light absorption by these deeply pigmented melanomas.

Unfortunately, there is no satisfactory quantitative method of determining in vivo the concentration and localisation of HpD in tumour tissue. Porphyrins are usually measured by the level of fluorescence emission; however HpD is not particularly fluorescent.[27] Experimental work has shown that the concentration of HpD is of the order of several micrograms per gram of tumour tissue at dosages of 3·0 mg/kg at 48–72 hours after injection. It may peak after a few hours and remain essentially constant for days. Variation occurs between different tumours in one patient and between different patients with the same kind of tumour. Moreover it may decrease with irradiation.[28] The poor correlation between tumour response to PT and volume, height, and energy dose may be due to variable uptake of HpD by tumour tissue. Newer photosensitisers may prove to be more suitable and overcome some of the problems of HpD.

At present there is no reliable method of calculating the most appropriate dose of light and HpD to obtain maximal tumoricidal activity with minimal damage to normal tissue. The effective absorbed dose depends on the light energy density at the dose point, the concentration of the photosensitising drug, and the concentration of molecular oxygen.[28] There is experimental evidence that the depth of tumour kill is directly related to the dose of light energy, rather than the concentration of HpD.[29] In this series higher doses of HpD (5–7·5 mg/kg) than previously reported for posterior uveal melanomas[16] were used, and all tumours were treated initially 24 hours after administration, as laboratory data indicated this to be the optimal time.[28] Because light energy densities above 200 J/cm$^2$ significantly increase the depth of tumour kill,[30] and eradication of posterior uveal melanomas by light energy densities in excess of 1500 J/cm$^2$ has been reported,[16] we aimed at about 1000 J/cm$^2$; total light energy levels averaged 960 J/cm$^2$ in our series.

The fluorescein angiographic evidence of tumour and choroidal vascular occlusion and elimination of fluorescein leakage for those melanomas which showed regression have also been observed following radiotherapy.[31] This supports the concept that ischaemia due to endothelial cell damage of tumour blood vessels is a possible mechanism of action of PT.[32]

Sunburn persisting for one or two days and presenting as an erythematous swelling of the skin, mainly of the face and hands, has been the major side effect in all patients. The commonest ocular complication in 14 patients (74%) following PT was a transient serous retinal detachment overlying the tumour, nine of which resolved in six weeks. This probably reflects the inflammatory response to the high laser energy levels used, and, in the five patients (26%) in whom the localised retinal detachment persisted, overlying vitreous traction was associated. Two patients (10%) developed anterior uveitis which resulted in pupil block glaucoma and subsequent cataract in one and an associated posterior scleritis in the other. A transient vitreous haemorrhage immediately following PT occurred in three patients (16%), all of which resolved without complication. Four eyes (21%) which showed no response to PT were enucleated, though no eye was enucleated for complications of PT. The post-treatment visual function was worse in 15 patients (79%). However, in 13 patients (68%) the tumour was located posteriorly and involved the macula, and in two patients (10%) the tumour was located in the temporal equatorial position, and the macula was involved secondarily from the retinal and choroidal vascular occlusion which followed PT.

At present no globe preserving treatment is entirely successful. The obvious advantages of PT are its non-invasiveness and repeatability. At this stage of development phototherapy may be a satisfactory treatment for small and medium size light to moderately pigmented posterior uveal melanomas, and as a supplementary treatment following recurrences with other methods.

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# Orbital lymphoma versus reactive lymphoid hyperplasia: an analysis of the use of computed tomography in differential diagnosis

S Westacott, A Garner, I F Moseley, J E Wright

**Abstract**

**Computed *x* ray tomography (CT) studies of 40 patients with proptosis or periorbital swelling, in whom biopsy showed lymphoma in 23 and reactive lymphoid hyperplasia in 17, were analysed in an attempt to identify radiological differences between the two conditions. The results indicate that homogeneity of an orbital mass is a sensitive but non-specific indication of lymphoma, 75% of lymphomatous masses and only 23% of reactive lesions being homogeneous. Bone destruction was seen only in cases of lymphoma, but was rare. Other radiological features of the mass or the affected orbital structures did not allow discrimination of tumour from a reactive lesion.**

Localised lymphocyte proliferation within the orbit, sufficient to cause proptosis or swelling and developing in the absence of an identifiable cause, is well recognised. However, this proliferation may be a reactive hyperplasia, presumed to be inflammatory and falling into the broader category of orbital granuloma or pseudotumour, or neoplastic, in the form of non-Hodgkin's lymphoma.[1] It is important to distinguish these two conditions to orientate appropriate treatment.

Although an early publication[2] indicated that computed *x* ray tomography (CT) was 'of little value in the diagnosis and management of lymphoproliferative diseases' of the orbit, this technique has now become the standard method of examination, providing a valuable means of investigating orbital masses, the orbital skeleton, and the surrounding soft tissue structures.[3] The differentiation between lymphoma and reactive hyperplasia, among the most common conditions causing patients to present with proptosis or periorbital swelling, has traditionally been on clinical grounds – reactive hyperplasia, like inflammation, tending to cause pain and lymphoma being relatively painless,[4] though the distinction is not absolute.[5] Response to systemic steroids can be confusing.[5] The 'non-specific' CT appearances have been described previously,[6] and little attempt has been made to differentiate benign from malignant lymphoproliferative lesions.[7 8]

*Table 1 CT characteristics of orbital masses*

| | *Lymphoma (28)* | *Hyperplasia (21)* |
|---|---|---|
| Size | | |
| 2 cm or less | 8 (29%) | 9 (41%) |
| 2 1–4 cm | 17 (61%) | 9 (41%) |
| more than 4 cm | 3 (11%) | 4 (18%) |
| Shape | | |
| round | 3 (11%) | 0 |
| moulded | 17 (61%) | 13 (59%) |
| irregular | 8 (29%) | 9 (41%) |
| Texture | | |
| homogeneous | 21 (75%) | 5 (23%)* |
| Site: | | |
| postseptal only | 4 (14%) | 4 (18%) |
| preseptal only | 1 (4%) | 1 (5%) |
| both | 23 (82%) | 17 (77%) |
| intraconal only | 3 (11%) | 1 (5%) |
| extraconal only | 21 (75%) | 15 (68%) |
| both | 4 (14%) | 6 (27%) |
| quadrant | | |
| superomedial | 15 (54%) | 12 (55%) |
| superolateral | 25 (89%) | 19 (86%) |
| inferomedial | 12 (43%) | 6 (27%) |
| inferolateral | 18 (64%) | 13 (59%) |
| Number of quadrants | | |
| one | 2 (7%) | 6 (27%) |
| two | 14 (50%) | 7 (32%) |
| more than two | 12 (43%) | 9 (41%) |
| mean | 2 50 | 2·27 |
| Extraorbital spread | | |
| intracranial only | 1 (4%) | 1 (5%) |
| extracranial only | 7 (25%) | 4 (18%) |
| both | 0 | 0 |

*$p<0{\cdot}01$

The aim of this study was to identify, without reference to the clinical or demographic data, radiological characteristics which might aid in differential diagnosis.

## Material and methods

### RADIOLOGICAL

The CT examinations of the orbits of 40 patients, comprising 50 abnormal orbits, were examined retrospectively. Since patients had been referred from several hospitals, there was no standard technique, but in general thin (2 mm) axial sections were obtained through both orbits in the plane of the optic nerves, targeted to include the pituitary fossa. Coronal images were obtained by scanning directly in the coronal plane or by computer reformation where axial sections were sufficiently thin; three patients had only axial images. Only contrast-enhanced images were obtained in the majority of cases: nine patients were examined without and three before and after intravenous contrast medium.

The histological diagnosis was not known by the radiologists at the time of review of the images, the criteria for which were as follows. The maximum diameter of the mass was measured, by means of the computer generated scale of the imager, to the nearest 5 mm; its shape was recorded as rounded, moulded to adjacent structures, or irregular; its margin as well or poorly defined and its texture as homogeneous or otherwise, regardless of the regularity of its borders. The overall radiographic density of the mass, compared with that of the adjacent brain, was noted before and/or after intravenous contrast medium, and the pattern of contrast

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*Table 2 Effects of orbital mass on normal structures*

| | *Lymphoma (28)* | *Hyperplasia (21)* |
|---|---|---|
| Globe: | | |
| displacement | 18 (64%) | 20 (91%) |
| distortion | 0 | 0 |
| incorporation | 0 | 0 |
| nil | 10 (36%) | 2 (9%)‡ |
| Optic nerve: | | |
| displacement or distortion* | 4 (14%) | 3 (14%) |
| incorporation† | 3 (11%) | 5 (23%) |
| nil | 21 (75%) | 14 (64%) |
| Lacrimal gland: | | |
| displacement or distortion* | 3 (11%) | 3 (14%) |
| incorporation † | 19 (68%) | 15 (68%) |
| nil | 6 (21%) | 4 (18%) |
| Muscles: | | |
| displacement or distortion* | 4 (14%) | 9 (41%) |
| incorporation† | 15 (54%) | 9 (41%) |
| nil | 6 (21%) | 4 (18%) |
| Number of muscles involved: | | |
| none | 6 (21%) | 4 (18%) |
| one | 8 (29%) | 8 (36%) |
| more than one | 14 (50%) | 10 (45%) |
| mean | 1·92 | 2·55 |
| Bone | | |
| remodelling | 3 (11%) | 1 (5%) |
| lytic destruction | 2 (7%) | 0 |
| thickening | 2 (7%) | 5 (23%) |
| nil | 23 (82%) | 16 (73%) |

*Excludes incorporation.
†Includes displacement or distortion.
‡$p<0·05$.

enhancement was recorded as uniform, inhomogeneous or focal. The site of the mass in relation to the orbital septum, muscle cone, and quadrant (superolateral, inferomedial, etc) was noted, together with spread outside the orbit superficially or towards the paranasal sinuses or cranial cavity. Involvement of normal orbital structures, such as the optic nerve or muscles, was assessed as displacement or distortion by the mass or incorporation into it. Effects on the bony skeleton were recorded as remodelling, lytic destruction, or thickening of bone. The orbital fat was assessed for evidence of focal or generalised alteration in radiographic density. The results were subjected to statistical analysis by the $\chi^2$ test.

### HISTOLOGICAL

Tissue was obtained by open biopsy under direct vision in all cases, fixed immediately in formol–saline, and subjected to histopathological examination. Sections were cut from paraffin embedded material and, in addition to conventional haematoxylin and eosin staining, were stained for the presence of Ig light chains $\varkappa$ and $\lambda$ by an immunoperoxidase technique. The criteria for recognition of neoplastic proliferation were based on a fairly uniform accumulation of lymphocytes with diffusely distributed immature cell forms, a dearth of other types of leucocyte, and a mono- or markedly oligoclonal light chain profile in the cytoplasm of the antibody-forming cells. Reactive lymphocyte proliferation was identified by the presence of germinal centres (though these were not invariable), of macrophages in moderate numbers and, less commonly, of eosinophils and neutrophils, and of a polyclonal light chain pattern. For the purposes of this study lesions which could not confidently be assigned to one or other group were excluded.

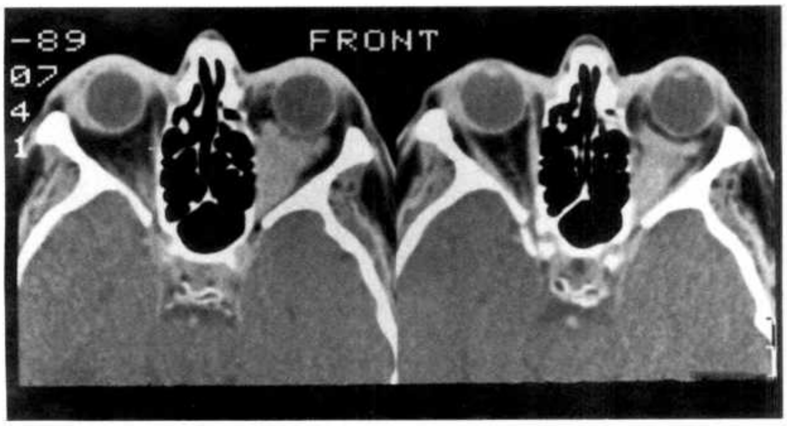

*Figure 1 Lymphoma of the left orbit: 2 mm contiguous axial CT sections after intravenous contrast medium (Somatom DRH, Siemens). The abnormal soft tissue is of homogeneous radiographic density.*

## Results

Tables 1 and 2 show the frequency of the radiological findings in the two disease groups, expressed as the numbers of abnormal orbits showing a particular characteristic. Some data are not included: insufficient patients were examined both before and after intravenous contrast medium for useful assessment of enhancement; there was no discernible alteration of fat density in any patient; all but one of the masses were well defined. Five (22%) patients with orbital lymphoma and five (29%) with reactive lymphoid hyperplasia had bilateral masses. Mucoperiosteal thickening, presumed to represent simple inflammatory change, was present in the paranasal sinuses of four patients (17%) with lymphoma and two (12%) with reactive disease.

## Discussion

The CT appearances of lymphoid orbital masses are well documented[9] and common manifestations of non-specific orbital inflammation have been described. Thus it is usually possible to distinguish inflammatory or reactive lymphoid masses from inflammatory changes in Graves' disease.[10] Several workers have suggested features which may discriminate inflammatory or reactive masses from lymphoma: scleral thickening[11] and infiltration of retrobulbar fat[12] are suggestive of the former, while remodelling or destruction of the orbital skeleton may suggest neoplasia.[1 13] In general, however, the appearances are too variable for accurate diagnosis, and biopsy is essential.[2 14]

In this study neoplasms (57%) showed a slight predominance over reactive hyperplasia, as in most large series; McNally *et al*[15] found 64 of 100 patients with orbital lymphoproliferative lesions to have lymphomas. Our CT findings were broadly in agreemnt with those of Yeo *et al*,[9] who did not, however, differentiate radiologically between the 15 cases of lymphoma and 12 of lymphoid hyperplasia in their series. Thus less than 10% of the masses were solely intraconal, and the majority involved several quadrants, superior lesions being more frequent than those lying below the globe. The masses tended to conform to the shape of the globe. It has been

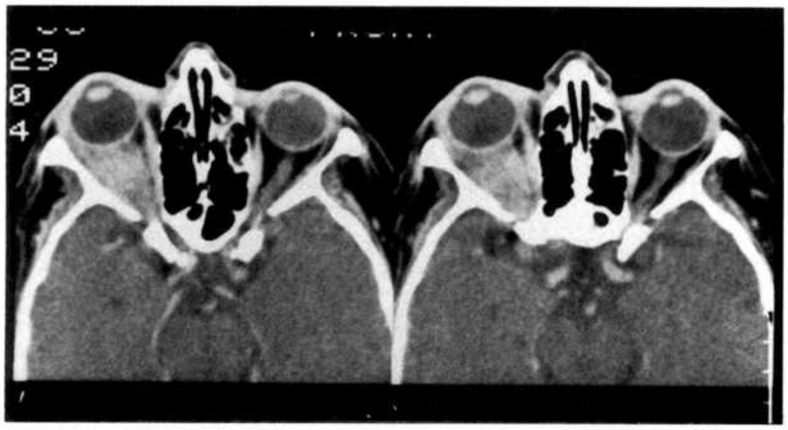

*Figure 2 Reactive lymphoid hyperplasia of the right orbit: CT as in Figure 1. The radiographic density of the mass lesion is more inhomogeneous, although the variability is not marked.*

suggested that, as the orbit itself contains no lymphatics, postseptal lesions are more likely to be neoplastic and preseptal lesions to be reactive,[16] but this was confirmed neither by our findings nor in a smaller series reported previously.[17]

It is evident from our findings that no single radiological feature is a reliable discriminator betwen lymphoma and lymphoid hyperplasia. Homogeneity of texture was significantly more frequent ($p<0\cdot01$) in patients with lymphoma (Fig 1) than in those with reactive lymphoid masses (Fig 2), in accordance with the reported finding of lower CT attenuation values in inflammatory masses than in lymphoma, attributed to inflammatory infiltration of the intraconal fat cells.[18] There are, however, several potential pitfalls in this observation: in all cases examined the degree of inhomogeneity was minor, and occasionally difficult to discern; the orbital soft tissue structures are particularly liable to streak artefacts and artefacts due to beam hardening and scatter, because of the adjacent bone; partial volume effects diminish resolution, tending to increase apparent inhomogeneity, especially with small masses. Nevertheless, if a standardised scanning technique is employed, the texture of the mass may provide a clue to the differential diagnosis.

Displacement of the globe was significantly more common ($p<0\cdot05$) in patients with reactive lymphoid lesions, but was frequent in both groups, since the presence of proptosis or periorbital swelling was one of the criteria for inclusion.

Although bone destruction may occur with other types of orbital pseudotumour,[2] among lymphoproliferative cases Knowles and Jakobiec[1] observed bone destruction only with malignant lymphoma; this was also the case in our series, but it was insufficiently common to be a useful finding, occurring in only two patients.

In one series lymphoid lesions affecting predominantly the extraocular muscles involved almost exclusively the superior rectus/levator palpebrae complex, and were mainly benign;[19] we confirmed the predilection for the upper orbit, but not the predominance of reactive lesions. Lacrimal gland involvement is also more commonly due to lymphoma than to lymphoid hyperplasia,[20] but our findings point to this being simply a manifestation of the relative frequency of the two conditions.

In common with previous workers we did not find bilaterality helpful for discrimination.[2,17] This is not surprising, since the proportion of patients with unilateral and bilateral lymphoproliferative lesions who subsequently develop lymphoma in other sites is identical.[15] No other radiological criteria were of discriminatory value, emphasising the fact that although orbital CT is of proved utility for orientating biopsy, planning radiotherapy,[21] and monitoring treatment, it is not useful in differential diagnosis.

Although a minority also advise local irradiation for benign lesions,[22] most workers reserve radiotherapy for malignant lymphoma when localised to the orbit.[23] Biopsy and immunohistochemical examination of the type described here thus remain essential.[17,24] While it is therefore convenient and, for the purposes of management, important to make a clear distinction between benign, reactive lesions and those which should be considered as malignant neoplasms, with potential for dissemination,[15] sometimes more than five years after the initial presentation,[25] this consideration should not obscure the possibility that lymphoproliferative orbital disease may represent a continuous spectrum. Thus there is evidence that lesions beginning as polyclonal reactive processes can succumb to malignant transformation with light chain restriction.[5] Moreover, it appears that a proportion of patients will have masses which, although initially presumed to be inflammatory, harbour a clone of neoplastic cells which will proliferate alongside the reactive lymphocytes.[26] Development of contralateral monoclonal lymphoma in a patient presenting with a polyclonal reactive lesion is also described,[15] and there are even reports, though poorly documented, of patients with benign orbital lesions who subsequently developed systemic lymphoma.[22] Such overlap would go some way to explaining the inability of radiological techniques to establish a reliable distinction between the two ends of the spectrum as specifically represented here: had more histologically indeterminate proliferations been included in the study, the degree of radiological differentiation would probably have been even more blurred.

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# Nitrous oxide and internal tamponade during vitrectomy

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## Abstract

**We analysed the nitrous oxide composition of the intraocular gas bubble following vitrectomy and fluid-air exchange in 12 patients. Samples were taken under standardised conditions at 20 minutes after completion of the fluid-air exchange. Analysis was conducted by a Medishield MS2 mass spectrometer. The percentage composition of nitrous oxide in the samples varied between 4 and 21% (mean 9%). This influx of nitrous oxide was associated with an increase of intraocular pressure. Pressure rises of greater than 20 mm Hg were not seen owing to venting of gas through the sclerostomies. An inverse relationship was noted between the extent of retinal detachment preoperatively and the amount of nitrous oxide entering the eye. A possible explanation for this relationship is proposed. The importance of nitrous oxide movement is stressed.**

Historically the movement of nitrous oxide into air-containing spaces in the body was first recognised during the 1950s when treatment for pulmonary tuberculosis included artificial pneumothorax. Interest in this phenomenon relating to ophthalmic practice increased following the 1973 Edward Jackson memorial lecture given by Norton.[1] Since then several studies have reported experimental results in animals, stressing the importance of nitrous oxide movement and its effect on intraocular pressure (IOP).

Wolf *et al* demonstrated both a rise in IOP[2] and an increase in volume[3] in the presence of neat intravitreal sulphur hexafluoride ($SF_6$) in cats maintained on nitrous oxide anaesthesia. Smith *et al*[4] working on rhesus monkeys demonstrated a similar rise in IOP when nitrous oxide was used to maintain anaesthesia in the presence of an intravitreal air bubble.

The inference from these studies has been that peroperative movement of nitrous oxide into a gas filled eye is potentially very important and has influenced vitreoretinal practice ever since. None of these studies, however, have quantified the nitrous oxide influx, and all have been performed on animals. We therefore decided to investigate this phenomenon further in a group of our patients.

## Materials and methods

Following the approval of the Ethical Committee and informed consent from the individuals concerned 12 American Society of Anesthetists Class 1 patients undergoing vitrectomy were recruited into the study. The details of the patients and indications for surgery are shown in Table 1. None of the patients had an abnormal intraocular pressure preoperatively. A standard anaesthetic technique was used in all cases. Anaesthesia was induced by intravenous thiopentone and muscle relaxation with atracurium. Anaesthesia was maintained by 65% nitrous oxide in oxygen and 1 to 2% enflurane with supplements of alfentanil and droperidol as required. Respiration was controlled to maintain the end-tidal carbon dioxide concentration at 4%. Residual muscle relaxation was reversed with glycopyrolate and neostigmine.

A standard 20 gauge, 3-port vitrectomy in combination with a fluid-air exchange was performed on 12 eyes of 12 patients. During the fluid-gas exchange the pressure in the eye was maintained at 25 mm Hg by means of a Greishaber air pump using filtered room air (Fig 1). Immediately on completion of the fluid-air exchange the instrument ports were sewn tightly and the infusion port connected to the manometer to allow repeated measurement of the IOP.

The eye was left undisturbed for 20 minutes, and IOP readings were taken every two minutes. At the end of the equilibration period a 1·0 ml sample of intravitreal gas was taken by means of a pars plana stab with a 25 gauge needle on a gas syringe. The IOP was immediately restored by means of the air pump. The sample was analysed by a Medishield MS2 mass spectrometer.

We had considered the factors known to influence gas transfer[5] and endeavoured to keep as many as possible constant. Agitation was avoided by leaving the eye for 20 minutes without interference, while variations in blood flow and partial pressure were minimised by a standardised anaesthetic technique and stable haemodynamic parameters during the study period. The solubility coefficient is constant for a given gas. However, the diffusion coefficient may vary, as for example in aphakic eyes, in which the surface of the iris is available for gas transfer as well as the retinal surface. Similarly, aphakia will influence the surface area of the bubble as will high myopia. Diffusion distance

*Table 1 Details of patients*

| *Patient* | *Age* | *Sex* | *Disease* |
|---|---|---|---|
| 1 | 62 | F | RRD |
| 2 | 12 | M | Trauma |
| 3 | 71 | M | RRD |
| 4 | 46 | M | RRD |
| 5 | 17 | F | Trauma |
| 6 | 66 | F | RRD |
| 7 | 60 | F | RRD |
| 8 | 44 | M | RRD |
| 9 | 41 | M | TRD |
| 10 | 69 | F | RRD |
| 11 | 32 | M | Trauma |
| 12 | 67 | F | RRD |

RRD=rhegmatogenous retinal detachment. TRD=tractional retinal detachment

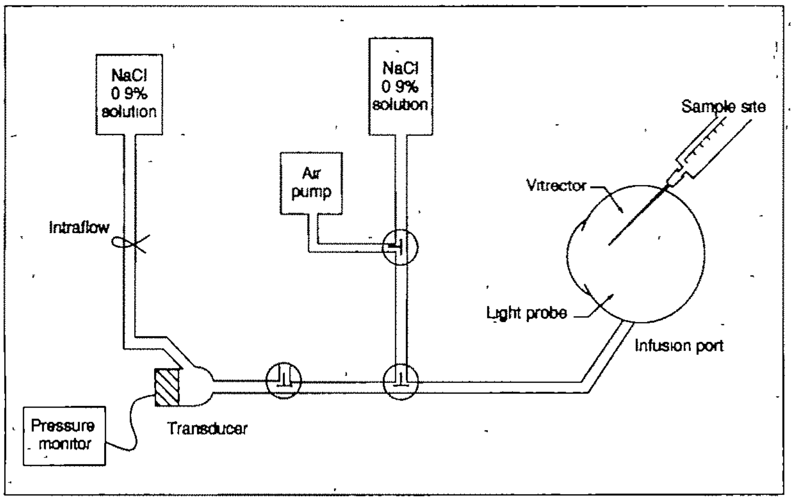

*Figure 1 Diagrammatic representation of apparatus.*

should not be a variable following complete fluid-air exchange.

We therefore analysed our results in terms of the following variables: phakic status, repeat surgery, recent cryo/laser therapy, duration of retinal detachment, extent of retinal detachment, and trauma.

## Results

### INTRAOCULAR PRESSURE

A consistent pattern was observed in all the eyes studied. The IOP rose steadily over the first few minutes to a peak level which was 18–20 mm Hg above the baseline. Thereafter no further rises occurred, but gas bubbles were noted to be escaping from the sclerostomy sites. In the last few minutes of the study period the IOP was frequently observed to fall back towards the baseline level.

### NITROUS OXIDE MOVEMENT

The percentage composition of nitrous oxide in the gas samples in each patient is shown in Table 2. The values ranged from 4 to 21% with a mean of 9%. The column on the right represents the number of quadrants of attached retina in each case. This was the only variable which showed a correlation with the percentage of nitrous oxide in the samples. We found no effect from any of the other parameters previously mentioned.

The correlation between the percentage composition of nitrous oxide and the number of quadrants of attached retina is shown in Fig 2 with the line of best fit. The correlation coefficient is 0·72, indicating that not all the variation is attributable to this factor. However, a $\chi^2$ test shows significance at the $p<0\cdot02$ level.

*Table 2 Results of nitrous oxide influx*

| *Patient* | *Disease* | *%N$_2$O* | *AR* |
|---|---|---|---|
| 1 | RRD | 5·0 | 1 |
| 2 | Trauma | 7·1 | 0 |
| 3 | RRD | 6·3 | 2 |
| 4 | RRD | 4·0 | 1 |
| 5 | Trauma | 21·0 | 4 |
| 6 | RRD | 7·4 | 1 |
| 7 | RRD | 6·3 | 2 |
| 8 | RRD | 12·0 | 3 |
| 9 | TRD | 7·1 | 3 |
| 10 | RRD | 9·3 | 2 |
| 11 | Trauma | 17·1 | 3 |
| 12 | RRD | 5·5 | 0 |

AR = quadrants of attached retina before operation.

No correlation between percentage of nitrous oxide, that is the extent of influx of the nitrous oxide, with the peak IOP during the study period was noted. This is presumably because of the uncontrolled and unquantified leakage from the sclerostomy sites which was apparent in all cases.

## Discussion

The influx of nitrous oxide into an air-filled eye during anaesthesia occurs because of the high partition and diffusion coefficients (0·468 and 2·6 respectively) of nitrous oxide. Equivalent values for nitrogen are 0·0147 and 2·01 respectively, and for sulphur hexafluoride are 0·004 and 1·16. These high values for nitrous oxide ensure a net influx into the bubble even though other gases such as nitrogen and carbon dioxide are leaving the eye down their concentration gradients. What then is the clinical effect of this influx of nitrous oxide? Theoretically there are two situations to consider.

(1) *Increment.* If the nitrous oxide is added to the intraocular bubble, the IOP must rise, and according to the gas laws this can theoretically cause pressures in excess of 100 mm Hg.

$$PV/T = \text{constant}$$

where P is in mm Hg atmospheric, and T is in degrees Kelvin. In our study we did record pressure rises of up to 40 mm Hg. However, above the level of 40 mm Hg the sclerostomies leaked, thereby preventing more serious pressure rises. These leaks occurred despite purposefully closing the sclerostomies tightly at the beginning of the period of study.

(2) *Displacement.* If the nitrous oxide simply displaces the other constituents it will result in a dilution effect; for example, 20% SF$_6$ (a commonly used non-expansile concentration) will be reduced to approximately 18%. This reduction will shorten the duration of action of the internal tamponade and may adversely affect the outcome of the surgery. Had the influx of nitrous oxide been relatively constant in all the cases

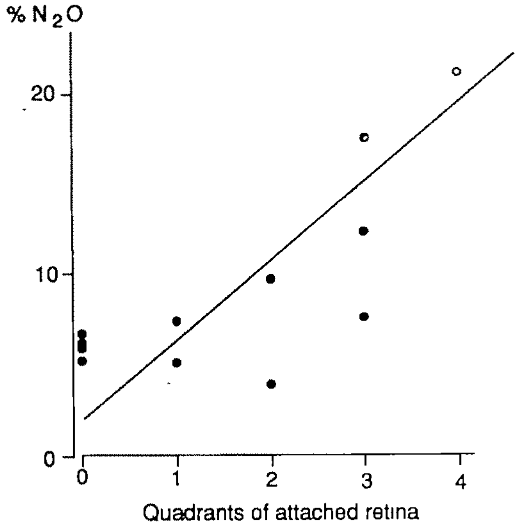

*Figure 2 Correlation between extent of preoperative attached retina and amount of nitrous oxide influx.*

studied, it would have been possible to compensate for the dilutional effect by using a higher initial concentration. As our results show, however, there was a great deal of variation in influx between cases (from 4 to 21%). Hence any estimate of the final concentration in any one case is unlikely to be accurate.

We consider that peroperative rises in IOP secondary to nitrous oxide movement are not of significance in vitrectomy because of the venting effect of the sclerostomies. At the end of the anaesthetic, however, the nitrous oxide leaves the eye as quickly as it entered, and this will result in a precipitous drop in intraocular pressure which cannot be compensated for by increased aqueous production or movement of nitrogen or carbon dioxide into the gas bubble. The dramatic nature of this efflux was shown in an experiment by Lincoff *et al.*[6] They found that nitrous oxide injected into the vitreous cavity of a cat was removed so rapidly when the animal was ventilated with air that the cornea became concave within 15 minutes.

The correlation coefficient of 0·72 in Fig 2 implies that there are other factors involved in the movement of nitrous oxide during anaesthesia. Their identification has not been possible owing to the small numbers in the present study; to identify them would require multivariate analysis and very large numbers of subjects. The inverse relationship between the extent of the detachment prior to the surgery and the percentage nitrous oxide in the samples suggests a definite trend. One possible explanation of this correlation is that gas transfer occurs more readily across retinal pigment epithelium which has maintained its normal anatomical and biochemical relationships. Mere physical reapposition of the retina and pigment epithelium, as occurs during a fluid-air exchange, does not appear to result in immediate recovery of function. This might have been expected, since it is well known that a detached retina does not recover its normal transparency for several hours following successful reattachment.

The question whether the anaesthetist should be asked to turn off the nitrous oxide during vitrectomy remains contentious. Our results have led us to conclude that nitrous oxide should be turned off, for two reasons. The first is because the nitrous oxide displaces an unpredictable amount of the other gaseous constituents, and the second because of the problems associated with a period of hypotony postoperatively, namely, plasmoid aqueous production with a fibrinous iritis, and choroidal detachment or haemorrhage.

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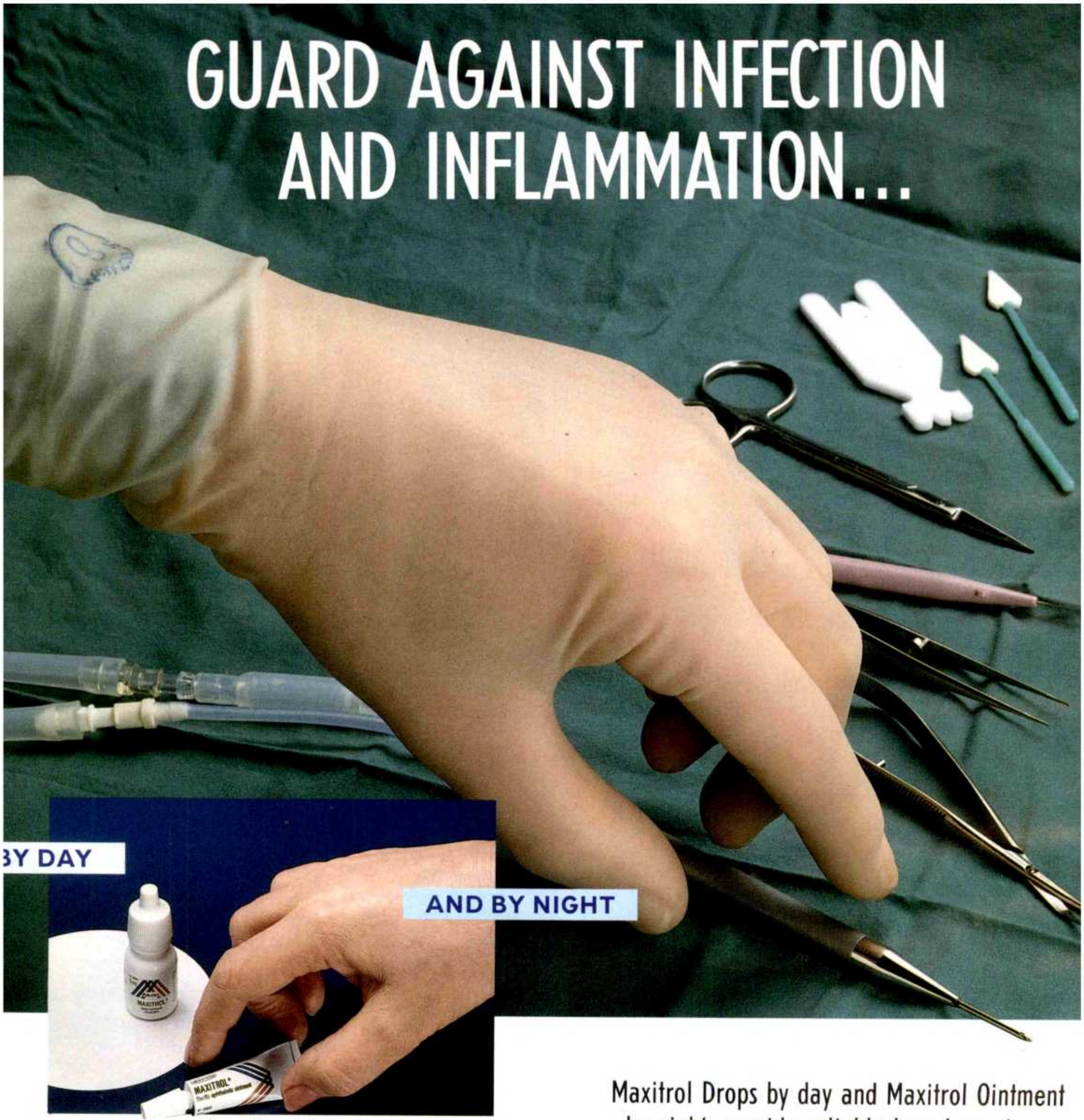

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# Treatment of iatrogenic choriovitreal neovascularisation in sickle cell disease

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## Abstract

**The effect of scatter photocoagulation on the perfusion of iatrogenic choriovitreal neovascularisation (CVN) has been assessed by a randomised trial in 35 CVN lesions in 18 eyes with proliferative sickle retinopathy. No difference in size or vascularity of CVN lesions was apparent between the nine treated and nine control eyes over a median follow-up of 42 months. Scatter photocoagulation by the stated protocol was not effective in the treatment of CVN.**

The vaso-occlusive process of sickle cell disease results in peripheral retinal ischaemia which may be associated with the development of proliferative sickle retinopathy (PSR). Treatment of PSR has been attempted by photocoagulation of the feeding arterioles in order to render these lesions avascular and therefore less prone to sight threatening complications. However, attempted closure of these feeding vessels requires high energy photocoagulation burns, which often disrupt Bruch's membrane. Ingrowth of choroidal vessels may result and is especially common following xenon arc photocoagulation.[1 2] Choriovitreal neovascularisation (CVN) has occurred in 53% of treated eyes.[3] Choriovitreal neovascularisation may of itself lead to sight threatening complications including vitreous haemorrage, retinal traction, and retinal detachment.[3 4]

Therapy of choriovitreal neovascularisation by direct photocoagulation of the lesion,[1 2] cryotherapy or transscleral diathermy[2] has been unsuccessful in achieving closure and has been associated with rapid enlargement of the lesion,[1] vitreous haemorrhage, and traction detachment of the retina.[2] In proliferative retinal vascular disease clinical evidence of a link between retinal ischaemia and retinal neovascularisation is well known. Hypotheses for the mechanism include the roles of retinal hypoxia, proteolytic enzymes on basement membrane collagen, insulin-like growth factors, and retina-derived growth factors.[5] On the assumption that these influences induce and maintain the ingrowth of choroidal vessels the effect of local retinal ablation has been investigated.

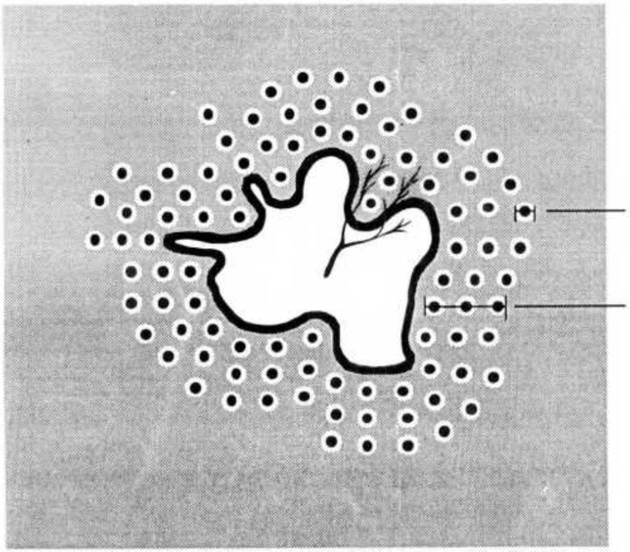

*Figure 1 Diagram of laser treatment pattern round chorioretinal scar containing choriovitreal neovascularisation.*

## Patients and methods

The patients attended the Sickle Cell Clinic at the University Hospital of the West Indies and had participated in two trials of xenon arc photocoagulation of PSR feeder vessels for which patients were enrolled during March 1973 to January 1977[6] and April 1978 to September 1980.[7] Eighteen patients (mean age 38·2 years, range 21–61 years) were admitted to the present trial; their admission was based on signs of CVN on ophthalmoscopy and fluorescein angiography. Ten patients had sickle cell-haemoglobin C (SC) disease, six homozygous sickle cell (SS) disease, one sickle cell-β† thalassaemia, and one sickle cell-β° thalassaemia. Each patient contributed one eye to the trial, with a total of 35 CVN lesions (single lesions in nine eyes, two lesions in four eyes, three in three eyes, four in a single eye, and five lesions in a single eye). The patients were recruited between March and September 1984; and after informed consent were randomly allocated to treatment or control groups by opening sealed envelopes. The nine eyes allocated to treatment contained 14 CVN lesions all of which were treated, and the nine control eyes contained 21 CVN lesions. All patients had assessment of corrected visual acuity, examination with indirect ophthalmoscopy, and fluorescein angiography concentrating on the early stages of dye transit to confirm the origin of blood supply for each CVN lesion.

The treatment protocol involved the creation of a 2–3 mm wide region of burns on the retina round the original burn scar but avoiding direct treatment to the CVN lesion, by applying argon laser burns of light to moderate intensity (212 to 584 in number, 400 µm size, 0·1–0·2 watt power, 0·05–0·1 second duration) spaced 1 burn diameter apart (Fig 1). Scars near the ora serrata, where burns could not be placed anterior to the lesion, were surrounded by a horseshoe of burns laterally and posteriorly. All treated patients were asked to attend for review within one week to check for early complications, and then at 3, 6, 9, 12, 15 months and at 3–4 years. One treated patient failed to attend for any review and could not be located. Three defaulted at, or had inadequate angiographic assessments after, nine months (control), 12 months (treatment), and 15 months (control). The remaining 14 eyes (seven treatment, seven control) were followed up for 3–4 years. In terms of individual CVN lesions no follow-up was possible for 4 CVNs; 4 CVNs were observed for 9 months, 4 for 12–15 months, and 23 for the 3–4 year period.

The outcome was assessed by changes in visual acuity and in perfusion on angiography. A drop in acuity of 2 lines or more on the Snellen chart (with Snellen lines 6/6, 6/9, 6/12, 6/24, 6/36, and 6/60) for two consecutive visits at least three months apart was regarded as significant. Angiograms were examined by stereoscopic technique. An independent examiner (ELC) examined the angiograms but not the eyes to reduce observer bias. The response was defined as progression (increase in number or size of the previous capillary bed), regression (a decrease of the above), and cure (non-perfusion).

## Results

In two control eyes vitreous haemorrhage reduced visual acuity, but this improved to normal with resolution of the haemorrhage within three months. The visual acuity in all other treated and control eyes remained unchanged.

Perfusion continued in all treated and control eyes. Of 11 CVN lesions in each group with angiograms adequate for assessment of capillary structure the vessel systems increased in size in two treated cases and four controls, and remained stable or decreased in size in nine treated cases and seven controls, the difference failing to reach statistical significance (Fisher's exact test, p=0·31).

## Discussion

The rationale of the trial was based on the concept that the maintenance of choriovitreal neovascularisation may depend on humoral factors released by adjacent ischaemic retina. This assumption derived from the analogy to the effect of scatter photocoagulation in causing regression of retinal neovascularisation in retinal vein obstruction,[8] and proliferative retinopathy associated with diabetes[9] and sickle cell disease.[10-12] The success of scatter photocoagulation in causing a prompt and sustained regression of choriovitreal neovascularisation developing after photocoagulation for choroidal melanomata[13] is also consistent with this concept, though effects are likely to be due to photocoagulation of the tumour as well as the retina.

The present study suggests that scatter photocoagulation, as conducted by the stated protocol, has no effect in reducing the vascularity of iatrogenic choroidal neovascularisation in proliferative sickle retinopathy. This could imply either that the area of treated retina was insufficient to reduce a humoral stimulus to choroidal neovascularisation, that such a humoral stimulus was unnecessary for the maintenance of choroidal neovascularisation, or that another source of stimulation (such as the retinal pigment epithelium or choroid) was unaffected. Indeed the role of such humoral factors in the development and maintenance of both PSR and CVN is still unclear. With the exception of the regression of CVN lesions formed in the treatment of choroidal melanomata[13] there is no evidence implying a humoral agent in the development or maintenance of CVN lesions.

Neovascular lesions arising from the choroid are difficult to render avascular: direct photocoagulation,[1,2] cryotherapy,[2] transscleral diathermy,[2] and scatter photocoagulation have all be unsuccessful. However, although these lesions may appear large and sometimes increase dramatically in size, their effect on ultimate visual function is incompletely documented. Sight threatening complications may occur but fortunately are infrequent.[3,4] The magnitude of risk to vision appears to be no worse than in eyes with PSR alone.[4]

Consideration of the potential complications of photocoagulation – for example, that this condition is iatrogenic – necessitate a conservative approach to this generally benign condition.

We thank Professor L Jampol and Mr P Condon for their advice in the conduct of this trial, Miss Susan Ford for her help with the photography, and Dr Mary Codd for statistical analysis.

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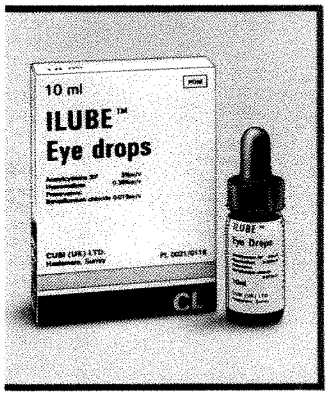

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# Daycase cataract surgery

N P Strong, W Wigmore, S Smithson, S Rhodes, G Woodruff, A R Rosenthal

## Abstract

**The increasing demand for cataract surgery, combined with limited resources, has created renewed interest in daycase admission. We have audited the results of all daycase and inpatient cataract surgery in a large unit over a six-month period to determine the factors influencing daycase admission and surgical outcome; 34% of cataract patients were admitted as daycases in the study period. Neither distance travelled by the patient nor age appear to influence daycase admission. However, the differing policies of the individual consultant surgeons resulted in a wide variation in the number of operations performed on a daycase basis by each firm. The rate of preoperative complications was unaffected by daycase admission, by the grade of surgeon operating, or by the type of anaesthetic employed. Only 2·1% of daycase admissions resulted in unplanned inpatient admission on the day of surgery, with another 2·1% being readmitted within six months of surgery. Late cancellation of surgery was much lower for daycases (0·4%) than for inpatients (5·1%).**

Twenty years ago a patient undergoing cataract surgery might spend two weeks in hospital.[1 2] In Britain an inpatient stay of only a few days is now usual, and in the United States 80% of cataract operations are now performed as daycases.[3] Factors that have contributed to this change in management include an increasing demand for cataract surgery,[4] the cost of extended inpatient care,[5] and a substantial drop in the number of elective surgical beds in the NHS.[6 7]

There have been several reports of daycase cataract surgery in the United Kingdom.[5 8 9] One unit has set up a small dedicated day unit;[5] all other reports concern patients managed in an inpatient ward. In the last year our department has elected to close an entire inpatient ward and set up a dedicated daycase unit. To analyse the impact of this major change we have audited the results of the first six months of operation of our daycase unit and have compared them with the inpatient ward in order to determine: (1) the factors influencing whether a patient is admitted as an inpatient or daycase; (2) the complication rate for daycases versus that for inpatients; (3) whether it is appropriate for junior surgeons (below consultant grade) to perform daycase surgery; (4) whether a significant number of unplanned inpatient admissions arise as a result of daycase surgery; and (5) the comparative rates of late cancellation of daycase and inpatient cataract surgery.

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## Patients and methods

The design of the ophthalmic daycase surgical unit (ODSU) and the medical and social criteria applied for patient selection for daycase cataract surgery are described elsewhere.[10] The cataract surgery inpatients were managed on a separate but adjacent ward.

Cataract surgery was performed under either general or local anaesthesia. Daycase operations that required either general anaesthesia or local anaesthesia augmented with intravenous sedation were restricted to morning lists. Local anaesthesia was achieved with either retrobulbar or peribulbar infiltration, with or without oral or intravenous sedation.

### SURVEY DESIGN

All patients admitted to the ODSU for cataract surgery over the first six months of its operation were entered on a database. All patients having cataract surgery as an inpatient during the same period were entered into a second database file. Patient data were obtained by examining the records of the ODSU, inpatient ward, operating theatre, and hospital computer. From these sources we obtained the patient's age, anaesthetic, consultant firm, surgeon operating and distance travelled to the hospital (derived from the postcode). In addition the individual hospital records of both inpatients and daycases were examined if (*a*) the operation was cancelled, (*b*) vitreous loss was noted in the threatre record. (*c*) an anterior chamber lens or no lens was implanted, (*d*) the patient was readmitted.

Any patients undergoing further surgery at the same time as cataract extraction, such as a trabeculectomy or keratoplasty, were excluded from this study.

Statistical analysis was by two sample *t* test $\chi^2$ test, and Fisher's exact test.

## Results

Two hundred and thirty six patients underwent standard cataract surgery as daycases, accounting for 34% of all cataract operations performed during this period. One further patient was admitted, but the operation was cancelled. The proportion of all cataract patients managed as daycases rose during the period under study from 29% in the first two months to 32% in the second and 38% in the last two months.

In the six months of this study 487 patients were admitted as inpatients, of which 462 had the operation performed (66% of all cataract operations) and 25 had surgery cancelled.

The daycase and inpatient cataract patients were compared to determine which factors might influence the decision to admit as an inpatient or daycase. Four variables were examined: the distance of the patient's home from the hospital, the patient's age; the type of anaesthetic used; and the identity of the surgical firm admitting the patient.

*Table 1 The percentage of all cataract operations carried out on a daycase basis by each of the consultant firms in the first six months of operation of the ODSU, and the relationship between the percentage of cataract surgery carried out under local anaesthesia and the percentage performed on a daycase basis for each of the consultant firms*

| *Consultant no* | *Percentage of cataracts as daycases* | *Percentage of cataracts under local anaesthetic* |
|---|---|---|
| 1 | 23 | 50 |
| 2 | 14 | 36 |
| 3 | 33 | 32 |
| 4 | 19 | 25 |
| 5 | 74 | 90 |
| 6 | 49 | 82 |
| 7 | 35 | 65 |

The distance that the patients travelled to hospital was very similar for the two groups (p=0·43), and averaged 10·0 miles (SD 9·4) for daycases and 10·5 miles (SD 9·6) for inpatients. Similarly the age distribution of the two groups differed little (p=0·26), with an average age of 71·9 years (SD 10·9) for the daycase patients and 72·9 years (SD 12·6) for the inpatients.

Daycase cataract surgery was more likely to be carried out under local anaesthesia (90% of operations) than was the case for the inpatients (56%). This difference is significant ($p<10^{-6}$).

Table 1 shows the percentage of cataract operations performed as daycase surgery by the different consultant firms. This varied from 14% to 74% of their total cataract workload, indicating a wide divergence in the surgeons' use of the daycase facility. Comparison of the different firms also showed a strong correlation between the proportion of cataract surgery carried out under local anaesthesia and the proportion of patients managed as daycases (Table 1).

A measure of the perioperative surgical complication rate was obtained by noting the number of cases of vitreous loss in each group. Table 2 shows vitreous loss rates for consultant and junior surgeons (that is, all surgeons below consultant grade) for daycases and inpatients. This shows that the junior surgeons performed more daycase surgery as a proportion of their total operative workload (41%) than did the consultants (26%). The rate of vitreous loss for daycases performed by juniors was slightly higher than for those done by consultants, but this difference was not significant (p=0·35), and for inpatients the consultant surgeons had the higher rate of vitreous loss, which again was not significant (p=0·14). Overall the rate of loss for all daycases (4·66%) did not differ significantly from that for inpatients (4·33%, p=0·49).

The vitreous loss rate for all local anaesthetic cases was 4·6% which was slightly higher than for general anaesthesia (4·2%), but not significantly (p=0·97).

Unplanned admission to the inpatient ward may be due either to a decision not to discharge on the day of surgery or to a subsequent readmission. Five patients were admitted as daycases but were then transferred to the inpatient ward (2·1% of all daycase cataract admissions). Two of these had been inappropriately accepted for daycase surgery despite not fulfilling the required criteria. Two others had vitreous loss during surgery and were kept in, and one was slow to recover from a general anaesthetic.

*Table 2 Vitreous loss rates for daycases and inpatients, according to grade of surgeon*

| | *Consultants* | *Juniors* | *All surgeons* |
|---|---|---|---|
| Daycases | 3/90 (3·3%) | 8/146 (5·5%) | 11/236 (4·7%) |
| Inpatients | 14/255 (5·5%) | 6/207 (2·9%) | 20/462 (4·3%) |
| All patients | 17/345 (4·9%) | 14/353 (4·0%) | 31/698 (4·4%) |

Another five daycase patients (2·1%) were readmitted at a later stage, all at least six or more days postoperatively. One developed endophthalmitis on the fifth postoperative day and was seen and admitted the following day. The second was admitted for repair of a small iris prolapse after a week. All the others developed late complications unrelated to daycase management. One fell and ruptured the cataract section three months postoperatively, and other patients were readmitted with retinal detachments three and five months postoperatively. No patient required immediate readmission or revision of surgery during the period under study.

Late cancellation of surgery is a major cause of wasted theatre time. Patients for daycase surgery are clerked in advance, so if a cause for cancellation or postponement of surgery is found there remains time to send for another patient. Consequently only one patient was admitted to the ODSU but then had surgery cancelled. This occurred because the notes had been mislaid (0·4% of admissions). In the same period 25 patients were admitted to the inpatient ward for cataract extraction but had surgery cancelled (5·1% of admissions). In two cases this was due to an infection contracted within a few days of the admission date and thus was unavoidable, and in three other cases there were problems with induction of local or general anaesthesia. However, for the other 20 patients (4·1%) the reason for cancellation was either that the patient had been inappropriately listed (seven patients) or was not medically fit for surgery (13 patients).

## Discussion

When the ODSU was first opened the intention was to manage at least 25% of cataract admissions as daycases, but during the first six months the ODSU was used for 34% of all cataract surgery admissions, and this rate rose over the study period, indicating an increasing acceptance of daycase cataract surgery among patients and staff.

Our hospital draws patients from a large area, and it might have been expected that geographic factors would affect the decision whether to admit as a daycase; however our data show this was not the case. Some daycase patients travelled over 30 miles each way. Nor did the patients' ages appear to influence management, as age distribution was identical for the two groups.

Of the factors examined the one having the most influence on the decision to perform cataract surgery on inpatient or daycase basis was the policy of the consultant surgeon concerned. Daycase surgery accounted for 74% of the total number of cataract operations performed by one of the consultant firms, whereas another performed only 14% of cataract operations in this way. Furthermore the proportion of operations performed as daycase surgery by each firm was closely related to the proportion of cases operated on under local anaesthesia (Table 1). Although a general anaesthetic did not preclude daycase admission, the restriction of general anaesthesia to the morning lists meant that any firm that did a high proportion of its surgery under general anaesthesia was not likely to be able to do most of its surgery as daycases. In Britain there is a tradition of general anaesthetic cataract surgery which differs from that of many other countries,[3] and which may have to be re-examined if daycase cataract surgery is to become more widespread.

The frequency of vitreous loss rate was adopted as a measure of peroperative surgical complications. This did not differ significantly between daycases and inpatients, even though a much higher proportion of the daycases were performed under local anaesthesia. Furthermore the vitreous loss rate for junior staff did not significantly differ from that of the consultant staff, and this would appear to justify the policy that all surgical grades should be allowed to undertake daycase surgery.

As the number of inpatient beds continues to decline it is important that unplanned overnight admissions are kept to a minimum. Of the 237 patients admitted to the ODSU for cataract surgery only five patients were kept in overnight afterwards (2·1%). Two of these were inappropriately listed for daycase surgery in the early days of the ODSU, and the listing procedure was amended to avoid repetition of these errors. Careful attention must be paid to patient selection for daycase cataract surgery, and it is essential that the patient understands the nature of the surgery and the type of anaesthetic that will be used. In addition adequate transport and social support must be available.

No patient required immediate readmission on being examined on the first postoperative day, and none required immediate revision of surgery. This is similar to the experience of Davies *et al*,[5] and it contrasts with an earlier report of short-stay inpatient surgery in which a substantial proportion of cases were readmitted or not discharged, some of whom required early reoperation.[11]

An argument against daycase surgery is that the recognition, diagnosis, and treatment of immediate postoperative complications may be delayed. However, the earliest a patient was readmitted was the sixth day following surgery, owing to an endophthalmitis which had developed over the previous 24 hours. As 94% of inpatients were discharged by the end of the third postoperative day this patient would most probably have been discharged prior to developing this complication even if managed as an inpatient.

It has been suggested that it is not appropriate to perform daycase cataract surgery under general anaesthesia,[12] and in previous reports daycase surgery has been performed exclusively under local anaesthesia.[8, 9, 13] However, 24 cataract daycase operations (10·2%) were carried out under general anaesthesia during the study period as well as 156 other operations.[10] Modern general anaesthesia now allows most patients to be fully ambulant on the day of surgery, and we believe that general anaesthesia as such is no longer a reason for inpatient management.

A subgroup of both inpatients and daycases having cataract surgery under local anaesthesia was studied in detail through the processes of admission, surgery, and follow-up and has been reported in preliminary form elsewhere (Rhodes S, proceedings of Age and Anaesthesia Meeting, Liverpool, April 1990). Among these patients it was found that there was no difference in patient satisfaction between inpatients and daycases, a finding in common with other studies (Lowe K, proceedings of Second Annual Congress of the College of Ophthalmologists, Harrogate, 1990). 80% of patients stated that they would be happy to repeat the experience, and there was no difference in this respect between patients operated upon with or without sedation. Most of the patients who were not happy were upset by matters not specific to daycase surgery, such as the hardness of the operating table or the claustrophobic sensation of the operating drapes.

Last minute cancellation of operations, for whatever reason, can result in a substantial wastage of theatre time. Only one patient (0·4%) was admitted to the ODSU but did not have cataract surgery. Twenty five patients (5·1%) inpatients had their surgery cancelled. In 20 of these inpatients the cause for cancellation would have been detected if the patient had attended a preadmission assessment clinic, such as that attended by the daycase patients.

The results presented in this paper derive from an audit, and patients were not randomised between daycase and inpatient management. Nevertheless our experience indicates that daycase cataract surgery is not associated with an increase in morbidity, and that this is true for patients who were operated upon by junior as well as by consultant surgeons. It results in fewer late cancellations than inpatient admission, is acceptable to the patients, and can be performed under general anaesthesia provided suitable guidelines are followed.

We are grateful to J Sparrow, FCOphth, for statistical advice and C Nicholson for editorial assistance.

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British Journal of Ophthalmology, 1991, 75, 734–736

# Climatic droplet keratopathy, exfoliation syndrome, and cataract

S Resnikoff, G Filliard, B Dell'Aquila

## Abstract

**During a countrywide survey we assessed the prevalence of climatic droplet keratopathy (CDK) in a randomised sample of 2446 subjects representative of the population of the Republic of Djibouti. The investigation of the relationship between CDK and two diseases considered to be related to exposure to ultraviolet light – namely, exfoliation syndrome and cataract – was planned as a case control study. In the rural area prevalence of CDK was five times higher than in the urban one (2·8% vs 0·5%) and varied according to districts. The highest rates were observed where the inhabitants' activities were related to the sea. The case control study revealed that the opacification of the lens was about three times commoner in patients with CDK than in patients without CDK ($p=0·03$) and that the exfoliation syndrome was about six times commoner in patients with CDK than in controls of similar age, sex, climatic conditions, and lens status ($p=0·02$). Moreover, we noticed that the sequelae of corneal perforations were about 30 times commoner in patients with CDK than in controls of similar age ($p<0·00001$).**

Climatic droplet keratopathy (CDK) is a corneal degeneration characterised by an opacification at the level of the Bowman's membrane. The earliest change to be seen is a fine collection of translucent droplets in the temporal and nasal aspects of the cornea within the area of the palpebral fissure. In more severe cases this droplet formation proceeds to cover the pupillary axis. Rarely, in the most severe cases, larger, golden droplets occur, a condition also known as 'spheroidal droplet degeneration'.

Since previous studies have shown that CDK might be linked to lens anomalies[1-3] we set ourselves two objectives: to assess the prevalence of CDK in a population based survey; and to study the relationships between CDK and other eye diseases considered to be related to ultraviolet light exposure, namely exfoliation syndrome and cataract.

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## Subjects and methods

The study was carried out on a representative sample of the Djiboutian population. The Republic of Djibouti is a country with an area of 23 200 km$^2$, situated in the horn of Eastern Africa. It has an estimated population of 470 000. Some 75% of the population live in urban areas, particularly in the city of Djibouti. The other 25% are basically nomadic in the semidesert hinterland and extend across the borders into Somalia and Ethiopa. The average annual rainfall is less than 125 mm. Life expectancy at birth was estimated to be 45 years in 1985 with an infant mortality rate of 200/1000 live births.

We used a two stage random cluster sampling[4 5] with two strata (rural and urban). The sampling frame consisted of the 1985 census. From a random start 65 sites ('clusters') were selected: 35 in the rural area and 30 in the urban one. Within each site we selected at random a starting point ('household'). Examination of all individuals began in the starting household and then continued to the next nearest one, until a total of 35 people had been examined. All individuals living in the last household falling into the sample were included even if the number was over 35.

In accordance with this methodology 2446 people were selected: 1117 in the urban sector (one inhabitant per 200) and 1329 in the rural one (one inhabitant per 50), making up a representative sample of the Djiboutian population.

The prevalence was determined on these two samples. To take into account the differences in age distribution we used a computational process known as standardisation (age and sex adjustment on WHO's African standard population).

The investigation of the relationship between CDK and cataract, or exfoliation syndrome, was planned as a case control study. The cases were all patients with CDK found during the survey; the controls were all adults aged 40 and above, taken from the samples. Aphakic patients were excluded from the case control study.

Confounding variables were neutralised in two ways: first, by Mantel-Haenszel's method. Age stratification was by 10 year age classes. Using narrower classes would not have been reasonable because of the absence of registration and the approximate nature of the patients' knowledge of their ages. Secondly, by matching on age, sex, and neighbourhood. Two controls were selected for each case according to the following method: same sex, same district, same age, or failing that (three cases) same age plus or minus five years. Whenever several individuals met these criteria, the two controls were randomly selected.

All ocular examinations were carried out by an ophthalmologist with a portable slit-lamp (Kowa SL5). The pupils of each person of 40 and above were dilated with one drop of tropicamide. When dilatation was inadequate this was repeated, and occasionally one drop of phenylephrine 5% was added. The lens of each eye was then re-examined with the slit-lamp and direct ophthalmoscope.

Cataract, if present, was classified into one of three stages (slight, partial, or complete) against the red glow of the fundus (Table 1).

When the severe grade of CDK was present

*Table 1 Definitions of categories of cataract*

0 *Normal.* No opacities detected
1 *Slight.* Less than a third of the red glow is obscure Details of the fundus are visible
2 *Partial cataract.* More than a third of the pupil area is obscure, but a partial red glow remains Only the optic disc and main vessels are visible
3 *Complete cataract.* No red glow visible

The presence and degree of lens opacities were judged by viewing through a direct ophthalmoscope and against the red glow of the fundus.[1]

*Table 2 Prevalence of CDK*

*Standardised rates (WHO's African standard population)*

Rural area: 36/1329=2·8% (1·7–3·7%)
Urban area· 6/1117=0·5% (0·22–1·31%)
Significant difference: *p<0 00001*
Odds ratio. 5·2 (2·1–13·6)
Age: 40 and above
Rural area 38/305=12·5% (9·1–16·9%)
Urban area: 4/198=2·0% (0·5–5 0%)
Significant difference *p=0·00003*
Odds ratio: 6·9 (2·3–23·1)

(six cases) and it was not possible to see clearly the centre of the lens with the eye looking straight ahead, the patient's gaze was directed downwards. It was then possible to examine the upper half of the lens, by looking through clear cornea over the band of keratopathy. Similarly the lower part of the pupillary area was seen with the eye turned upwards. Lastly, slight lateral or vertical movements made with the ophthalmoscope allowed us to differentiate between the shadow cast by keratopathy and the lens opacities.

## Results

### PREVALENCE

In the rural sector the prevalence of CDK was five times higher than in the urban (2·8% vs 0·5%) (Table 2). Moreover, the prevalence rates varied according to districts, the highest rates having been observed where inhabitants' activities were related to the sea (Table 3).

### CASE CONTROL STUDY

Four hundred and ninety six people aged 40 and above were selected: 41 cases and 455 controls (seven aphakic patients were excluded from the study) (Table 4).

The analysis did not reveal any association between CDK and sex, but showed a marked relationship with age (Table 5).

There was a significant association between various grades of cataract and the presence of CDK, even after stratification by age (Table 6). This relationship was confirmed after matching by age, sex, and neighbourhood: opacification of the lens was about three times commoner in patients with CDK than in patients without CDK (Table 7). Nevertheless, this relationship ought to be carefully interpreted, particularly because of the bias introduced by inaccurate knowledge of age, and also on account of confounders such as nutritional, socioeconomic, and occupational factors.

A strong relationship was found between CDK and exfoliation syndrome. In the case control study exfoliation syndrome was about 10 times commoner in patients with CDK (Table 8). However, the exfoliation syndrome and CDK

*Table 3 Geographical distribution; standardised rates*

| *District* | *Prevalence* |
|---|---|
| Obock | 6 1%* |
| Ali-Sabieh | 2·4%* |
| Tadjourah | 2·3%* |
| Dikhil | 2 0%* |
| Djibouti (rural) | 1·0%* |
| Djibouti (city) | 0·5% |

*p<0 01

*Table 4 Distribution, by 10-year age classes, of CDK cases and controls*

| *Age* | *No* | *CDK cases* | *Controls* |
|---|---|---|---|
| 40–49 | 238 | 4 (2%) | 234 |
| 50–59 | 175 | 18 (10%) | 157 |
| 60–69 | 62 | 14 (23%) | 48 |
| 70–80 | 20 | 4 (20%) | 16 |
| Total | 495 | 40 | 455 |

*Table 5 Case control study. Age: 40 and above, rural+urban areas. No=496 (209 males and 287 females): 41 CDK (cases) and 455 controls*

| | | |
|---|---|---|
| *Sex* | | |
| Males: | 18/209=8·6% | $\chi^2$=0·06, p=0·8 |
| Females. | 23/287=8·0% | |
| *Age* | | |
| CDK | average=57 years (SD 8·2) | |
| Controls: | average=48 years (SD 8·4) | |
| Analysis of variance: F(1,501)=40, *p<0·00001* | | |

*Table 6 Association between CDK and cataract; stratification by 10-year age classes*

| | | | *Categories of cataract* | | | |
|---|---|---|---|---|---|---|
| *Age* | | *No* | *0* | *1* | *2* | *3* |
| 40–49 | CDK+ | 4 | 50% | 50% | 0% | 0% |
| | Controls | 234 | 95% | 3% | 1% | 1% |
| | | | | *p<0 0001* | | |
| 50–59 | CDK+ | 18 | 55% | 28% | 0% | 17% |
| | Controls | 157 | 71% | 7% | 6% | 6% |
| | | | | *p=0 02* | | |
| 60–69 | CDK+ | 14 | 7% | 21% | 21% | 50% |
| | Controls | 48 | 42% | 25% | 14% | 19% |
| | | | | *p=0 02* | | |
| 70–80 | CDK+ | 4 | 0% | 25% | 0% | 75% |
| | Controls | 16 | 31% | 19% | 6% | 44% |
| | | | | *p=0 02* | | |

Age adjusted analysis of association between CDK and cataract (grades 1+2+3 vs grade 0) by Mantel-Haenszel method Mantel-Haenszel weighted odds ratio=3 91 95% confidence limits=1·77–8·63. Mantel-Haenszel summary $\chi^2$ 10 91, p=0·0095

*Table 7 Association between CDK and lens opacification. Matching for age, sex, and neighbourhood (lens opacities=cataract categories 1+2+3)*

| | *Lens opacities* | | *No lens opacities* | |
|---|---|---|---|---|
| | *No* | *%* | *No* | *%* |
| CDK | 30 | 73% | 11 | 27% |
| Controls | 43 | 51% | 40 | 49% |

$\chi^2$ (Yates' correction)=4 3, *p=0·03* Odds ratio=2·6 (1 1–6·1)

*Table 8 Association between CDK and exfoliation syndrome (ES)*

| | *No* | *% with ES* |
|---|---|---|
| *1 Case control study* | | |
| CDK. | 6/41 | 14·6% |
| Controls· | 8/455 | 1 75% |
| Fisher's exact test *p=0 0004* | | |
| Odds ratio=9 6 (2 7–32 7) | | |
| *2 Matching for age, sex, and neighbourhood. Stratification by cataract·* | | |
| Adjusted $\chi^2$ (Mantel-Haenszel)=4·9, *p=0 026* | | |
| Cataract-adjusted odds ratio for ES=6 4 (1·2–33 1) | | |

*Table 9 Association between CDK and sequelae of corneal perforations; case control study*

| | *No* | *% with sequels* |
|---|---|---|
| CDK | 5/41 | 12% |
| Controls· | 3/455 | 0·7% |
| Fisher's exact test *p=0 0003* | | |
| *Stratification by age* | | |
| Adjusted $\chi^2$ (Mantel-Haenszel)=27 7, *p<0 00001* | | |
| Age adjusted odds ratio=31 82 (8 8–115·2) | | |

are both related to age, climatic conditions, and probably cataract. Moreover, these three factors are also interrelated among themselves and form three counfounding variables which it is necessary to control to study the true relationship between CDK and the exfoliation syndrome. After matching for age and climatic conditions, and after adjustment for cataract, a significant association between CDK and the exfoliation syndrome was still observed: the odds ratio was 6·4, that is, the exfoliation syndrome was about six times commoner in patients with CDK than in controls of similar age, sex, climatic conditions, and lens status.

Even though this was not among our study objectives, while going through our data we noticed that a significant proportion (12%) of CDK patients had been recently afflicted by a non-traumatic, widespread corneal ulceration, leading to adherent leucoma or phthisis bulbi after perforation. On the other hand, out of the 455 controls only three were seen to have this type of lesion (which represents 0·7% of the controls). Thus a highly significant association existed between CDK and ulceration: sequelae of corneal perforations were about 30 times commoner in patients with CDK than in controls of similar age (Table 9).

## Discussion

The results obtained from this survey lead to a first evaluation of CDK prevalence in the Republic of Djibouti. They confirm its high level of occurrence in this part of Africa. Moreover, this is where it was described for the first time by Bartolucci in 1933.[6]

In comparison with central Africa its prevalence here is higher: 2·8% vs 1·7% in northern Chad (standardised rates).[2] In fact the prevalence of CDK seems to vary according to living conditions, ranging from 6% in seaside dwellers to 0·5% in city dwellers living a short distance away and sharing the same climatic conditions. Thus what was observed in Chad over an extensive area was observed also in Djibouti, where a large city, vast stretches of desert, a coast line and high mountains all come together within a few square kilometres.

The relationship between CDK and the exfoliation syndrome had already been found in Chad during a cross-sectional survery, but it was less evident in a case control study done in Somalia.[1] On the contrary, the alterations of the anterior lens capsule as described by Johnson *et al*[1] in Somalia were not observed anywhere in Djibouti during our survey. However, we did come across cases of herniation or lens capsule bagging among the patients of the ophthalmological department of the General Hospital of Djibouti (four out of 230 cases, that is 1·7%), but this was even less frequent in Chad.

As for the relationship between CDK and glaucoma, no study of it was possible owing to the small size of the sample.

Matching and adjustment techniques lead us to believe that relationships observed between CDK and cataract do not depend solely on age and climatic conditions. On the contrary, it appears that eyes affected by CDK should be considered as 'high-risk eyes' which need to be kept under close observation, especially with regard to glaucoma.

Finally, as for perforating ulcerations, which seem to pose a real threat to these patients, it would be useful to do some thorough research, particularly with the aetiological aspects in mind.

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# Natural history of treatment of facial dyskinesias with botulinum toxin: a study of 50 consecutive patients over seven years

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## Abstract

**To determine the long-term efficacy of botulinum toxin injections for the treatment of facial dyskinesias we studied 50 consecutive patients with blepharospasm, hemifacial spasm, and Meige syndrome. All received their first injection between September 1983 and June 1984. A total of 520 injections were given; the average number of injections per patient was 10·4 over the seven-year period ending September 1990. Twenty-six (52%) of the patients continued to return for periodic injections, while three patients no longer receive injections since they failed to respond adequately to treatment. Three patients with blepharospasm were in remission and required no further treatment, after a series of six, four, and three injections. Six patients were treated until they died of causes unrelated to facial dyskinesia or its treatment. Six patients are still being treated elsewhere because they could obtain injections closer to their homes. Five of the original 50 patients have been lost to follow-up. A patient with hemifacial spasm had one injection with good result but was not sufficiently bothered by her disease to return for reinjection. Complications were transient, minimal, well tolerated, and did not increase with increased number of injections.**

Several studies have established the relatively short-term efficacy of botulinum toxin (Oculinum injections) in the treatment of blepharospasm, hemifacial spasm, and Meige syndrome.[1-15] However, the long-term acceptance by patients of this treatment has not been as well documented.[16-18] In Kraft and Lang's study, the follow-up period for 76 patients who were treated with Oculinum injections was 10 to 36 months.[16] In Elston's series of 101 patients the mean follow-up period was 26·7 months with a range of 1 to 51 months.[17] Dutton and Buckley's study of 230 patients included 30 patients who had 10 or more treatments over a 51-month follow-up period.[18] We reviewed the first 50 consecutive patients of a total series of 302 treated to date in order to understand the natural course of facial dyskinesias treated with botulinum toxic type A over a seven-year period. The minimum follow-up period for all patients was 75 months.

## Patients and methods

Charts from the first 50 consecutive patients with blepharospasm, hemifacial spasm, and Meige syndrome treated with botulinum toxin injection were reviewed. Data analysed included age of onset, dosage, number of injections, treatment additional to botulinum injections, and complications. Patients no longer treated were contacted by telephone. All 50 patients were initially treated between September 1983 and June 1984. Of these 50 patients 31 were female and 19 were male. Thirty-three patients had blepharospasm, 13 had hemifacial spasm, and four had Meige syndrome (Table 1). The examination and injection techniques have been previously described.[5 13] All patients received the American product of botulinum toxin, Oculinum, rather than the British product, Dysport.

The initial treatment consisted of 5 units of botulinum toxic injected in divided doses into the medial and lateral portions of the pretarsal orbicularis muscle of the upper eyelids, and 5 units into the corresponding medial and lateral parts of the lower eyelids; and additional 2·5 units was injected into the lateral canthus. Patients with brow spasms received 5 units in two separate injections into the procerus muscle of the medial brow. Patients with facial spasms were given 5 units in two separate injections into the cheek area just below the malar eminence after having received eyelid injections. When examined two weeks after injection the patients with a poor response received an additional 10 units (double dose) in each upper lid.

## Results

Fifty patients received a total of 520 injections between September 1983 and September 1990. The mean age of the patients at the onset of their disease was 56·5 years (range 37–76) for blepharospasm, 62·5 years (range 40–76) for hemifacial spasm, and 72·3 years (range 52–64) for Meige syndrome. The average number of injections per patient was 10·4 over the seven-year period.

Of the original 50 patients 26 (52%) continued to return for periodic injections. The patients who continued to receive injections included 18 of 33 patients with blepharospasm, seven of 13 patients with hemifacial spasm, and one of four patients with Meige syndrome. The mean number of injections was 15·3 for 18 patients with blepharospasm, 11·3 injections for seven

*Table 1 Sex distribution by diagnosis of 50 patients*

| | *No of patients* | *Male* | *Female* |
|---|---|---|---|
| Blepharospasm | 33 (66%) | 12 (32 2%) | 21 (67 8%) |
| Hemifacial spasm | 13 (26%) | 5 (28 5%) | 8 (61 5%) |
| Meige syndrome | 4 (8%) | 2 (50%) | 2 (50%) |

*Table 2 Follow-up data on 50 patients by diagnosis*

| *Treatment status* | *Blepharospasm* | *Hemifacial spasm* | *Meige syndrome* | *Total* |
|---|---|---|---|---|
| Still treated | 19 | 6 | 1 | 26 (52%) |
| Treatment no longer required | 3 | 0 | 0 | 3 (6%) |
| Treatment failures | 1 | 1 | 1 | 3 (6%) |
| Treated until died | 1 | 4 | 1 | 6 (12%) |
| Treated elsewhere | 4 | 1 | 1 | 6 (12%) |
| Lost to follow-up | 5 | 0 | 0 | 5 (10%) |
| Good treatment response but no longer injected | 0 | 1 | 0 | 1 (2%) |

patients with hemifacial spasm, and 11·3 for the patient with Meige syndrome. The mean duration of action of the injections was 14·9 weeks for 18 patients with blepharospasm, 16·3 weeks for seven patients with hemifacial spasm, and 11 weeks for the one patient with Meige syndrome.

Three patients no longer receive injections since they failed to repond to periodic injections of botulinum. One such patient with blepharospasm responded to the initial injection but failed to respond to subsequent injections on five separate occasions at higher than standard dose levels. A second patient with Meige syndrome had only a partial response to initial injection and did not return for further treatment. A third patient, a 40-year-old male with left-sided hemifacial spasm, was treated from January 1984 to May 1987. The first seven of 10 treatments produced excellent results that lasted 14 to 18 weeks. The last three injections lasted 10, seven, and four weeks respectively. A neurosurgical consultation was obtained and in October 1987, he underwent a left retromastoid craniotomy with microvascular decompression of the seventh nerve, with good result. A third patient with blepharospasm received one injection and did not improve; she did not wish to return for reinjection.

Three patients with blepharospasm required no further treatment after a series of six, four, and three injections, respectively. Two of these patients have been in remission for over six years and the third patient for over five years.

Six patients were treated until they died of causes unrelated to facial dyskinesia or its treatment. Six patients are still being treated elsewhere because they could obtain injections closer to their homes. Five of the original 50 patients have been lost to follow-up. A patient with hemifacial spasm had one injection with good result but was not sufficiently bothered by her disease to return for reinjection (Table 2).

Six patients who continue to be treated had excision of excess skin with plication of the levator aponeurosis without effect on the duration of the injections. One patient with hemifacial spasm developed a basal cell carcinoma of the lower lid which was excised; another patient with hemifacial spasm had a marginal rotation of the right upper lid prior to injections. The duration of effect of the injection was not influenced by the surgery. These eight patients continued to be treated at expected intervals and received a mean of 14·1 injections without diminution of effect.

Six of 50 patients, all with blepharospasm, received a double dose in the upper lids (10 units) in each upper lid, and one patient received a quadruple dose (20 units) in the upper lid. Twenty-four of 50 patients received bilateral brow injections (5 units in each brow). Four patients with Meige syndrome received facial injections that varied in dosage from 5 to 20 units; one patient received 10 units in the masseter muscle for jaw spasms. All such patients also received eyelid injections. Three of the patients with hemifacial spasm received 5 units in the cheek.

Two of the patients who continue to receive injections are concurrently administered minor tranquillisers by their physician.

No complications, transient or mild, increased with the number of injections. In addition no patient withdrew from treatment owing to complications.[6 13] Tearing, the most common complication, was either due to weakness of the lacrimal pump or was reflex in nature due to lagophthalmos or to pre-existing dry eye (18 patients or 36%). The latter group of patients often had a concomitant foreign body sensation in the involved eyes. Tearing generally lasted one to two weeks and rarely up to six weeks from the time of injection; symptoms were relieved by topical lubricants and by increased voluntary blinking. Other complications were mild ptosis (seven patients or 14%), ectropion (one patient or 2%), entropion (one patient or 2%), and double vision (one patient or 2%). The patient with lower lid ectropion had hemifacial spasm; recurrent ectropion was prevented by injecting one-half the usual dose (2½ units) into the lower lid. The patient with double vision had received a double dose of Oculinum in the upper lid; he had temporary diplopia in upgaze in four of eight injections; the double dose was necessary for a duration of effect of 10 to 11 weeks.

## Discussion

The short-term effectiveness of botulinum toxin type A injection for the control of facial dyskinesias, including benign essential blepharospasm, hemifacial spasm, and Meige syndrome, has been well documented in several studies.[1-15] The percentage of patients who respond has varied from 93%[16] to 97%.[13] The study with longest follow-up period consisted of a cohort of 30 of a total of 230 patients who had 10 or more treatments over a 51-month follow-up period.[18] The natural history of a group of patients who have had botulinum toxin injections over a long period has not been elucidated.

The present study covered 50 consecutive patients with a minimum follow-up of over 75 months. The relatively high proportion of patients (52%) that continue to receive injections over the seven-year period strongly supports the debilitating nature of the facial dyskinesias, the patient's need for treatment, and the efficacy of botulinum toxin.

The low number of long-term failures, three of 50 patients, is again consistent with other studies with shorter follow-up. One of the three patients failed to respond after having had seven prior successful injections, and the other two patients responded to the initial injections but failed to respond to subsequent treatments. These findings suggest that clinically active antibodies rarely develop to the toxin, at least over a seven-year period. The data show that, if a given patient responds to two or more injections, tolerance to the drug will be unlikely to develop subsequently. Possibly longer durations of treatment and higher doses used in the treatment of other conditions such as torticollis may lead to tolerance.[19] Antibody studies are worth undertaking. Our study provides no evidence that the orbicularis muscle weakens from repeated injections over time to the extent that lower dosages of toxin are effective.

As in studies with shorter follow-up periods, complications were all transient, minimal, well tolerated, and did not increase with increased number of injections. These complications included tearing, ptosis, and rarely ectropion, entropion, and double vision.

Eight of the patients had eyelid surgery, including plication of the levator aponeurosis and repair of dermatochalasis (six patients), marginal rotation of the upper lid (one patient), and excision of a basal cell carcinoma of the lower lid (one patient). These eight patients continued to be treated at expected intervals and received a mean of 14·1 injections without diminution of effect. Our findings suggest that eyelid surgery may be safely performed without affecting treatment response.

Surprisingly, three of the 50 patients were in remission and no longer required treatment after a series of six, four, and three injections. To our knowledge remission after botulinum toxin injections is extremely rare and has not been previously reported. In a series of 264 patients with blepharospasm five were in remission for periods of one to six years without any treatment.[14] Such remissions suggest that blepharospasm may be self-limited in rare cases with or without treatment. The possible role of the drug, if any, in causing the remission is unclear.

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# More than meets the eye: a study of the time lost from work by patients who incurred injuries from corneal foreign bodies

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## Abstract

**A prospective study was carried out to establish the time lost from work due to corneal foreign body injury. Data were collected over a 5 month period on a total of 504 patients attending a busy district hospital eye casualty department. The median time lost through injury was 4 hours and 148 patients (30%) took no time off work. Corneal foreign bodies are known to be painful injuries but in spite of this few patients take more than half a day off work.**

All corneal foreign bodies are potentially sight threatening; the cornea may become scarred or distorted and intraocular infection may set in. Moreover the injury is characteristically painful and the patient may be put to a good deal of inconvenience and lose time from work.

Recent correspondence has suggested that employers may incur considerable costs through employees losing time from work.[1] This study provides details of the time patients lost from work. To our knowledge there are no figures available in the literature on this.

The opportunity was also taken to establish the source of these injuries.

The casualty department at Southampton Eye Hospital provides a 24 hour accident and emergency service for the general public in South West Hampshire. The resident population served by this hospital is approximately 420 000 although this number increases considerably during the summer months due to the popularity of the New Forest and the sailing facilities on the Solent.

The department is staffed by two senior house officers (SHOs) during the morning and one on-call SHO to cover the remainder of the day and the following night.

Trained nurses who have qualified with the English National Board (courses 346 and 348) examined and assessed all patients. The extended role of the nurse is currently practised in this department and a high proportion of patients receive emergency treatment carried out by members of the nursing staff.[2]

## Patients and methods

A prospective study was carried out in the casualty department of the Southampton Eye Hospital over a 5 month period. Information was collected on 504 patients who presented with corneal foreign body injuries.

Patients included in this study presented to the department from 12 January 1990 to 30 May 1990. An invitation to take part in the study was extended to all patients attending during this period. Each patient was given an outline of the study to read. The introduction asked if the patient would be willing subsequently to receive a telephone call to establish the time lost from work due to injury. Queries were dealt with by the duty SHO or the research sister and those patients unwilling to be contacted had this fact entered on their casualty card. These patients were not contacted later but details of their injuries were included in the findings of the study and the analyses of the results. Written consent to take part in the study was not considered necessary by the local ethical committee.

Data were collected daily by the duty SHO and details were transferred from the casualty record card to a study proforma. The following information was recorded on all patients: age and sex, occupation, date, time and place of injury, activity at time of injury, use and type of any eye protection, type of foreign body, the amount of time lost from work, and whether the patient was an employee or self employed. The proforma was completed following a telephone conversation with the patient and all data were entered on a computerised database. Statistical advice was taken prior to the study being undertaken and 500 was considered to be a suitable number of patients for statistical analysis. The time lost from work was calculated using the median due to a high percentage of patients with 0·0 hours lost. The $\chi^2$ test was used to indicate the statistical difference between the number of patients wearing eye protection when carrying out various activities. The Mann-Whitney test was used to show whether the self employed group took less time off work than those in employment.

## Results

During the 5 month study period a total of 504 patients attended the department with corneal foreign body injuries. Of these, 496 were male and eight female. The mean age was 35 years for males and 36 years for females. The age range of male patients fell between 6 and 75 years (Table 1).

The greatest number of patients took no time off work and only 37 patients lost more than 12 hours (Table 2). The figures show a true representation of hours lost from work for they include both the time spent in the casualty department and time for travelling to and from the hospital. There was no significant difference in the time lost from work between the self employed and employee groups.

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*Table 1 Age range of patients*

| *Age range* | *Number* |
|---|---|
| *Male* | |
| 6–10 | 5 |
| 11–15 | 1 |
| 16–20 | 35 |
| 21–25 | 65 |
| 26–30 | 84 |
| 31–35 | 72 |
| 36–40 | 69 |
| 41–45 | 65 |
| 46–50 | 33 |
| 51–55 | 32 |
| 56–60 | 16 |
| 61–65 | 9 |
| 66–70 | 2 |
| 71–75 | 1 |
| *Female* | |
| 20–25 | 1 |
| 26–30 | 1 |
| 31–35 | 3 |
| 36–40 | 1 |
| 46–50 | 1 |
| 55–60 | 1 |

*Table 2 Hours lost from work (total number of patients 407)**

| *Time lost (hours)* | *Number of patients* | *% of total* |
|---|---|---|
| 0 | 148 | 36·3 |
| >1<2 | 21 | 5·1 |
| >2<3 | 55 | 13·5 |
| 4 | 47 | 11·5 |
| 6 | 5 | 1·2 |
| 8 | 87 | 21·3 |
| 12 | 7 | 1·7 |
| 16 | 26 | 6·4 |
| 24 | 4 | 0·3 |
| 32 | 2 | 0·5 |
| 36 | 1 | 0·2 |
| 40 | 2 | 0·5 |
| 48 | 1 | 0·2 |
| 80 | 1 | 0·2 |

* 97 patients were unable to be contacted.

*Table 3 Hours lost from work in different activities*

| *Type of activity* | *No. of patients* | *Median* | *Range of hours lost* |
|---|---|---|---|
| Under vehicles | 24 | 4 | 0–24 |
| Other metalwork | 24 | 4 | 0–16 |
| Unknown | 75 | 4 | 0–16 |
| Drilling | 28 | 3·5 | 0–80 |
| Welding | 22 | 3·5 | 0–40 |
| Grinding | 67 | 3 | 0–32 |
| Hammering | 12 | 2 | 0–36 |
| Sanding/sawing | 12 | 2 | 0–12 |
| Near machinery | 22 | 2 | 0–16 |
| Misc. industrial | 44 | 2 | 0–24 |
| Windblown | 47 | 1 | 0–40 |
| Leisure | 29 | 0 | 0–32 |

*Table 4 Comparison of eye protection worn in work and home injuries (total number of patients 314)*

| | *Work* | *Home* |
|---|---|---|
| Wearing goggles | 82 | 5 |
| Wearing specs | 25 | 2 |
| No protection | 165 | 35 |

The median time lost from work by 407 patients was 4 hours (Table 3); 148 patients (30%) presented to the department out of working hours.

The majority of injuries occurred at work and most of the patients in this group did not wear any form of eye protection (Table 4).

The largest group was of patients who were unaware of how the foreign body entered the eye; grinding was responsible for the second largest number of injuries (Table 5).

The categories of activities and the number of patients who had protected and unprotected eyes in each group are shown in Table 6. A statistically significantly ($p<0\cdot05$) larger number of patients engaged in grinding and welding wore eye protection compared with those working on or under vehicles.

*Table 5 Activities at time of injury*

| *Type of activity* | *No of patients* |
|---|---|
| Unknown | 98 |
| Grinding | 89 |
| Windblown | 58 |
| Miscellaneous industrial | 51 |
| Leisure | 41 |
| Drilling | 30 |
| Welding | 28 |
| Working near machinery | 27 |
| Other metalwork | 24 |
| On or under vehicles | 21 |
| Hammering | 14 |
| Sanding and sawing | 11 |
| Total number of patients | 492 |

There was no information regarding activities of 12 patients

*Table 6 Comparison of eye protection worn in different activities*

| *Activity* | *Protection worn* | *No protection* | *Unknown* |
|---|---|---|---|
| Grinding | 61 | 22 | 6 |
| Windblown | 5 | 36 | 17 |
| Miscellaneous industrial | 14 | 30 | 7 |
| Leisure | 3 | 22 | 7 |
| Drilling | 6 | 24 | 0 |
| Welding | 21 | 5 | 2 |
| Near machinery | 3 | 21 | 3 |
| Other metalwork | 8 | 15 | 1 |
| On/under vehicles | 5 | 22 | 0 |
| Hammering | 1 | 13 | 0 |
| Sanding/sawing | 6 | 8 | 1 |

When possible the types of foreign body removed were identified and recorded. There was a predominance of metallic substances accounting for 56% of the total (unidentified types 32%, wood 2·5%, brickdust 2·5%, paint 2%, insects 1·5%, vegetable matter 1·5%, grit 1%, and dust 1%).

Attempts to telephone patients proved time-consuming and not altogether successful. The following were the reasons for failure to contact patients: 62 had no telephone, 15 numbers were unobtainable, nine no reply (after three attempts), eight patients were unwilling to participate in the study, two had moved away from the area and there was one wrong number recorded.

## Discussion

A study by Vernon[3] at the Bristol Eye Hospital showed that 33% of the cases of trauma were due to corneal foreign body injuries and an earlier study carried out in this department showed that corneal foreign body injuries were responsible for 26% of the total trauma attendances.[2] We initially assumed that there would be a high proportion of patients losing a considerable amount of time from their employment. It was therefore surprising to discover that the largest group of patients took no time off work and only a few patients took more than one full working day. Consequently we do not accept the assumption made in the study carried out at Moorfields Eye Hospital that patients take 2 days off work because of their injury.[4] Many of our patients indicated that it was more convenient for them to visit casualty out of working hours. Several patients pointed out that the reason they did not lose time from work was because their employers arranged alternative work for them until their vision had recovered. A number of patients in the self employed group admitted returning to work immediately after treatment but resumed a more office based sedentary type of role as opposed to a skill which required 'normal' vision.

This survey shows a predominance of young men at work among the patients studied and it is at this group that preventive measures should be aimed. Our results give cause for concern over the injuries which occur in spite of eye protection being worn at the time of injury (as illustrated by those carrying out grinding – see Table 5). This leads us to question both the effectiveness of protective wear and also whether the patients carry out the instructions and guidelines for their use. Harker *et al*[1] stated that injuries are preventable by using the appropriate type of protection but clearly the number of injuries occurring while the eye is apparently protected shows a need for the reinvestigation of the design and suitability of protective wear. Several patients in the miscellaneous industrial activity group mentioned that their injury occurred during the removal of their goggles or spectacles which led to particles dropping off their hair into their eyes. This may indicate that some form of head cover may be required for certain tasks in addition to the eyes being protected. We agree with the comments of others[4] on the problems of protective devices misting up, being uncomfortable, and being easily scratched. Many patients said that protective wear remained effective for a relatively short time and that it was too expensive to keep replacing it. Only very few patients said that employers ensured that eye protection was worn.

It is a pleasure to thank Mr M J Absolon FRCS, Mr C R Canning FRCS, Mr I H Chisholm FRCS, and Mr J I McGill FRCS for allowing us to study patients under their care. We are indebted to the Nursing Staff of the Casualty Department and Miss J Webb of the Medical Records Department for their help and also the patients without whom the study would not have been possible.

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British Journal of Ophthalmology, 1991, 75, 743–745

# A simplified technique for removal of orbital hydatid cysts

Gehad E Nahri

**Abstract**

**A surgical technique is described for cryoextraction of the inner germinal layer of orbital hydatid cysts. The technique was adopted in two cases. It is simple and effective and causes minimal postoperative reaction or complications. There were no recurrences over a period of 24 and 18 months respectively.**

Hydatid cysts of the orbit are formed round the migrated larvae of *Taenia echinococcus*. The disease is not rare in the Middle East and North Africa.[1-3] The diagnosis of orbital hydatid cysts presents problems and requires uncertain procedures such as blind aspiration, cystography,[2] or contrast orbitography.[4] Even then the diagnosis was rarely achieved preoperatively.[1-5]

The surgical removal of orbital hydatid cysts is frequently complicated. Cyst rupture is rather common and may result in a severe postoperative reaction anaphylaxis, incomplete removal, or secondary implantation.

## Patients and methods

### CASE 1

A male child aged 6 years presented in January 1987 with unilateral painless proptosis of the left eye of a few months' duration. Ultrasonography revealed the presence of a well demarcated cyst in the lateral orbit with minimal internal echoes (Figs 1, 2). A CT scan revealed a well localised cyst with radiolucent content and a regular wall that showed mild enhancement on contrast injection (Fig 3). The absence of past or present sinusitis, the lack of evidence of inflammation,

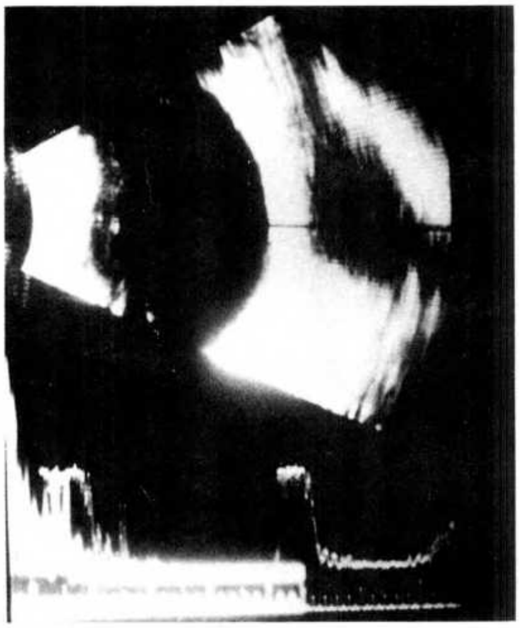

*Figure 1 Case 1. Sonogram showing sonolucent orbital cyst.*

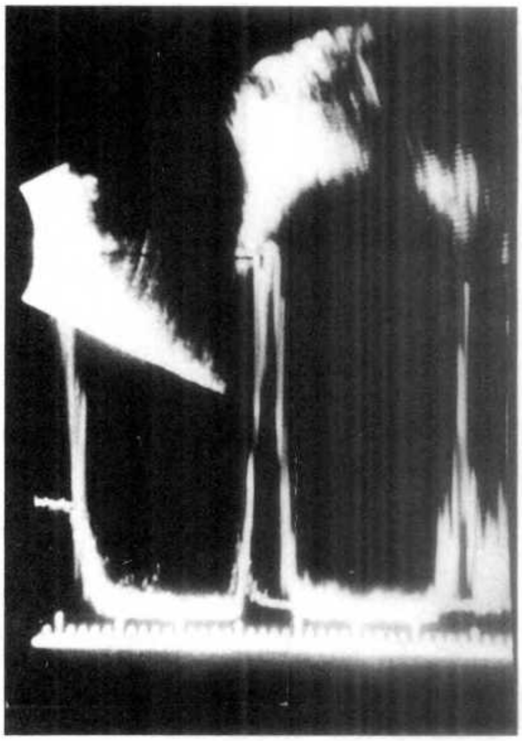

*Figure 2 Case 1. Sonogram showing sonolucent orbital cyst.*

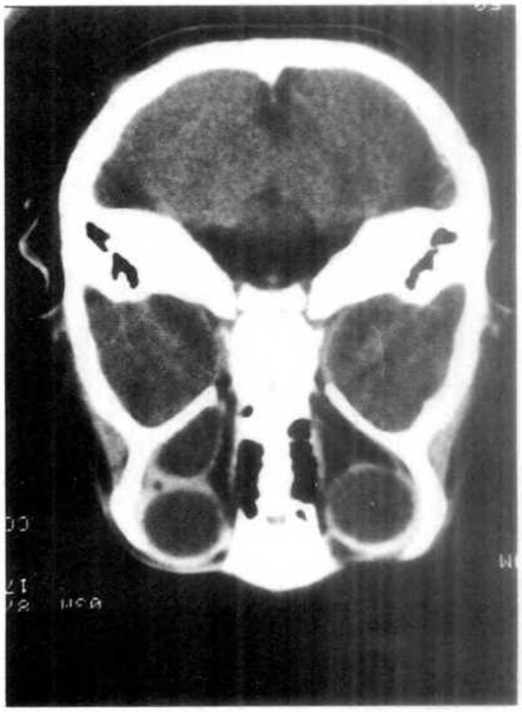

*Figure 3 Case 1. CT scan showing radiolucent cyst with mild enhancement of the wall.*

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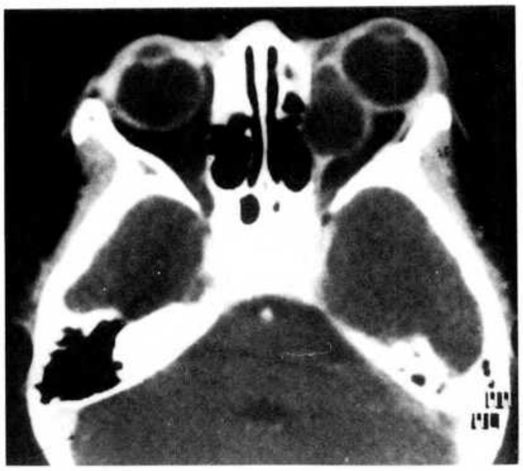

*Figure 4 Case 2. CT scan appearance.*

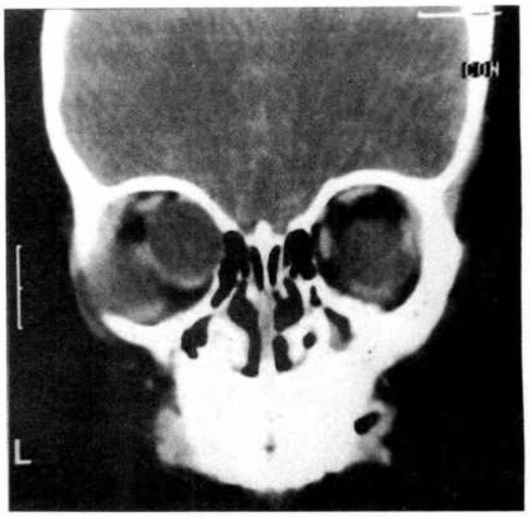

*Figure 6 Case 2. CT scan appearance.*

the regularity of the wall, and the mild enhancement with contrast excluded an orbital abscess. The very low internal reflectivity on ultrasonography, the complete radiolucency of the contents, and the location in the lateral orbit (which is a rare site for deep dermoids) suggested orbital hydatid cyst as the most likely diagnosis.

CASE 2

A female child aged 4 years had a few months' history of unilateral proptosis affecting her left eye. She had no pain. The conjunctiva was red and chemotic. The globe was deviated outwards, and fundus examination revealed disc oedema. CT scan was done (Figs 4, 5, 6), and the preoperative diagnosis of hydatid cyst was made from the characteristic features described above.

TECHNIQUE

The adopted technique allows the exposure and extraction of an orbital hydatid cyst without risking injury to important orbital structures. The technique lends itself to any of the surgical exposures used in orbital surgery and markedly reduces the length of orbital incisions.

Sharp and blunt dissection together with appropriate haemostasis and retraction are used until the outer fibrous wall of the hydatid cyst (ectocyst) is exposed over an area of 1×1 cm. A sharp disposable 27 G needle on a syringe is gently introduced into the cyst cavity, and as much as possible of the hydatid fluid is aspirated. The aspiration causes the inner germinal layer of the cyst (endocyst) to collapse, so that the outer fibrous wall is easily tented with a non-toothed forceps over the site of the needle puncture and snipped open. The opening is carefully enlarged for a length of 5–10 mm to reveal the whitish, glistening germinal layer. The endocyst is touched with an insulated cataract cryoprobe, and the probe is activated. The slippery germinative layer is easily and completely extracted through the opening (Fig 7). The outer fibrous wall is left behind, thus eliminating the necessity for extensive and frequently dangerous orbital dissection.

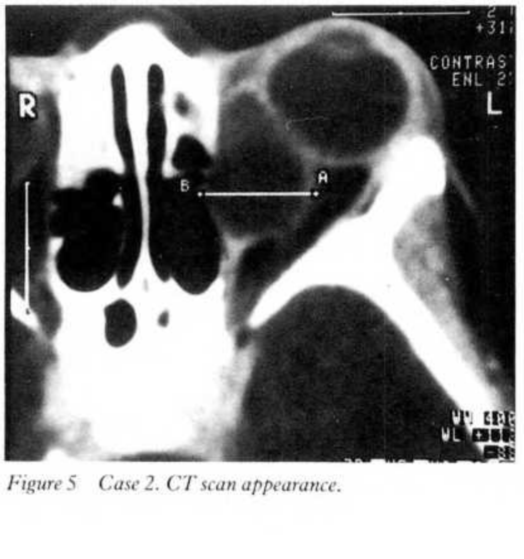

*Figure 5 Case 2. CT scan appearance.*

## Results

In two cases orbital hydatid cysts were removed by employing this technique. Owing to the limited exposure needed, the transconjunctival approach was used in both cases with no difficulty.

There were no operative complications, and the postoperative reaction was minimal. There were no recurrences over a period of 24 and 18 months respectively. No postoperative enophthalmos was observed.

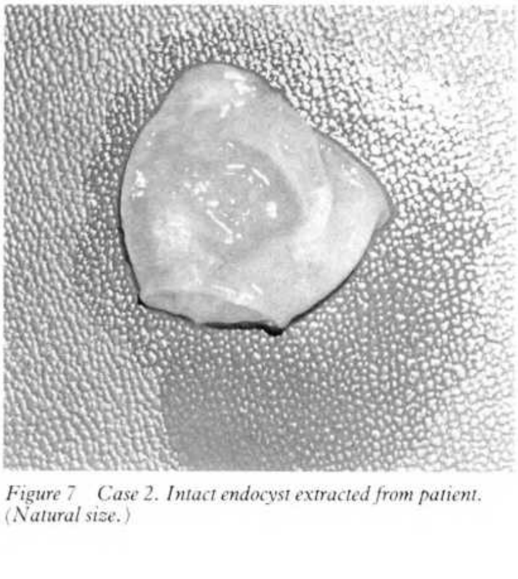

*Figure 7 Case 2. Intact endocyst extracted from patient. (Natural size.)*

## Discussion

Among 20 cases of proptosis in children seen in our department over the past 24 months there were two cases of hydatid cyst. Most reports on orbital hydatid cyst have concluded that a preoperative diagnosis is rarely established. These reports were of cases in which ultrasonography and CT scan were not used in reaching the diagnosis. We believe that the findings presented by these investigations may point to the diagnosis.

Surgical removal of orbital hydatid cyst is frequently complicated by cyst rupture.[3 5] This is mostly related to the extensive dissection done on the relatively tight orbits of children and the frequently thin wall of young cysts. Intraoperative aspiration of the cysts presents the following advantages: confirming the preoperative diagnosis, reducing the size of the cyst, and causing the inner germinative layer to collapse so that the outer fibrous wall is safely tented and snipped open. The enophthalmos frequently observed after removal of large orbital space-occupying lesions is avoided by leaving behind the outer fibrous wall of the cyst.

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*British Journal of Ophthalmology*, 1991, **75**, 746–748

# Visual development in the blepharophimosis syndrome

M Beaconsfield, J W Walker, J R O Collin

**Abstract**

**One hundred and one cases of the blepharophimosis syndrome presenting over a decade are reviewed with particular attention to the factors influencing their visual development. Three distinct clinical patterns emerge – severe bilateral ptosis, moderate bilateral ptosis, and asymmetric ptosis – and their differing incidence of amblyopia and strabismus is discussed. The risk of amblyopia is much higher than previously believed (56·4% in our series) and preventive management is discussed.**

The blepharophimosis syndrome is characterised by a narrowed horizontal palpebral aperture, ptosis, telecanthus, and epicanthus inversus. We have reviewed 101 cases presenting over 10 years with a minimum two-year follow-up to assess whether the often severe degree of ptosis and the epicanthic folds predispose to the development of amblyopia and strabismus.

## Materials and methods

One hundred and one patients who presented between 1978 and 1988 for an oculoplastic opinion on their blepharophimosis syndrome were reviewed. The minimum follow-up time was two years. The ocular examination included measurement of the horizontal and vertical palpebral aperture, levator function, telecanthus, severity of epicanthic folds, refraction, and results of orthoptic examination including the presence of amblyopia, ocular movements and alignment, state of binocular vision by the usual methods including the 4 dioptre and 15 dioptre prism, and stereo tests.

All the patients received a full ophthalmic and orthoptic assessment at each visit. The frequency of the visits depended on the age of the patients and the results of the orthoptic examination.

All patients of preschool age had cycloplegic refraction with spectacle correction if necessary. Visual acuity was assessed according to age and co-operation.

Any child found to have amblyopia possibly attributable to the ptosis was treated as a surgical emergency with a brow suspension procedure. This was accompanied by occlusion and spectacle correction, if appropriate, as with any case of amblyopia.

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## Results

All 101 patients were diagnosed as suffering from the blepharophimosis syndrome at or around birth. Forty four were female and 57 were male. Thirty one had a family history of the condition, with a 5:1 predominance on the father's side.

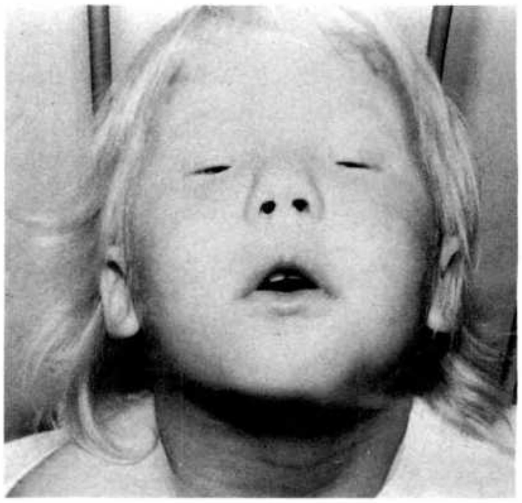

*Figure 1 Severe bilateral ptosis.*

Twenty seven cases presented for oculoplastic opinion by the age of 18 months and a further 25 cases before the age of 5 years. Therefore over half our cases presented before starting school.

Three distinct patterns of ptosis emerged. The patients were therefore grouped for analysis into those with severe bilateral ptosis, those with moderate bilateral ptosis, and those with asymmetric ptosis. Each group was then assessed in terms of amblyopia, refractive error, and telecanthus.

Thirty four patients had severe bilateral ptosis with palpebral apertures of less than 4 mm (Fig 1). Over half these patients (19 cases) had bilateral amblyopia, as defined by a visual acuity of 6/12 or less, which could not be improved with spectacle correction. Of these 19 cases 10 also had strabismus, of whom three had no refractive error, three had equal refractive error, and four were anisometropic. Among these 10 cases there were five patients with telecanthus greater than 35 mm (Fig 2).

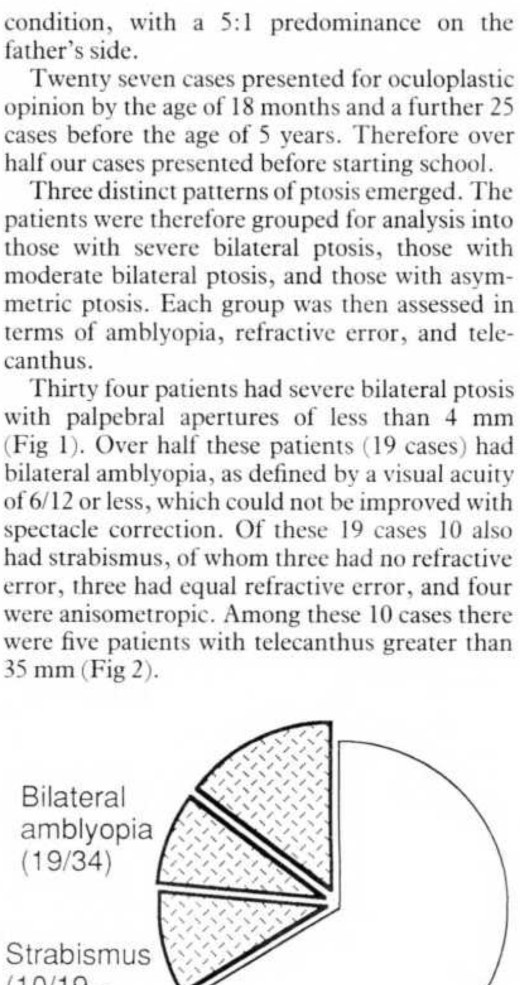

*Figure 2 Severe bilateral ptosis, 34 cases of 101.*

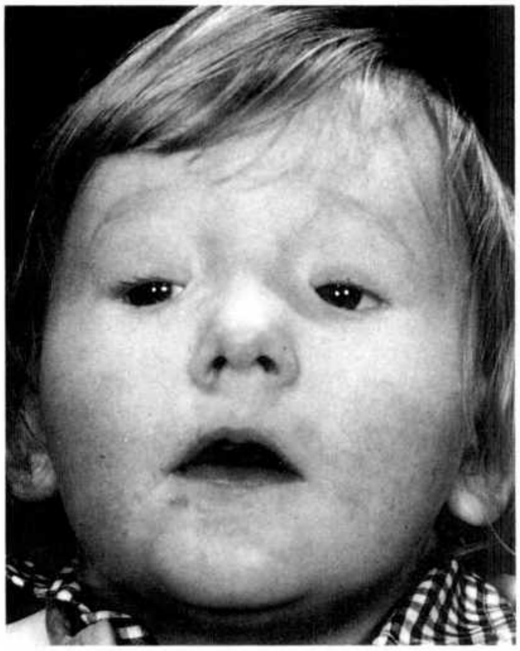

Figure 3 Moderate bilateral ptosis.

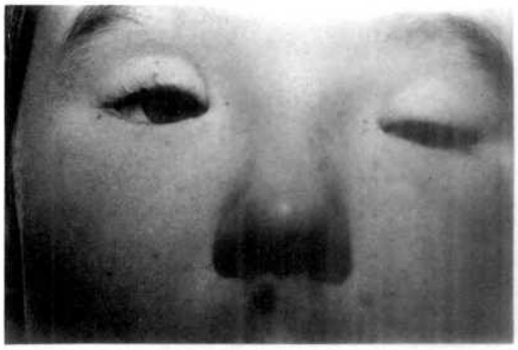

Figure 5 Asymmetric ptosis.

Forty patients had moderate bilateral ptosis with palpebral apertures of more than 4 mm (Fig 3). Even in this group 17 were amblyopic and all of these had squints. Ten were anisometropic and seven either had no refractive error (three patients). The remaining 23 patients had normal visual acuity in both eyes and no squint (Fig 4).

Twenty one patients had asymmetric ptosis where the pupil of one eye was intermittently covered during waking hours according to the examiner, the parent, or an independent witness (Fig 5). All were amblyopic in that eye but none had squints (Fig 4).

Twenty one patients had asymmetric ptosis where the pupil of one eye was intermittently covered during waking hours according to the examiner, the parent, or an independent witness (Fig 5). All were amblyopic in that eye but none had squints. A further six patients had asymmetric ptoses but the pupillary axis was clear. These were not amblyopic and had no significant refractive error (Fig 6).

The type of strabismus in approximately three-quarters of cases was convergent, some with an associated vertical element, usually a 'V' phenomenon.

Seventy two cases had moderate telecanthus (29–34 mm) and 29 were severe (35+ mm). Asymmetric telecanthus (2 mm or more) was noted in only three cases, of which only one was amblyopic with a convergent squint. This patient had an asymmetry of 7 mm with dense amblyopia on the more affected side, though the eyelid was not covering the pupil, and there was no significant refractive error.

The strabismic and amblyopic patients underwent regular refraction and patching followed by squint surgery as necessary. Of the 57 amblyopes (two lines or more), 13 failed to improve. Of these patients five presented as adults and already had established amblyopia; four presented between the ages of 6 and 9 years and did not cooperate with patching (three had bilaterally moderate ptosis with hypermetropic astigmatism and one was educationally subnormal with severe bilateral ptosis.). Three failed to improve with occlusion therapy and developed noncentral fixation, and one was lost to follow-up for over 18 months but reappeared with an established squint. He had a bilateral moderate ptosis with normal refraction.

Surgical intervention was carried out either to prevent amblyopia or for cosmesis. In cases of bilateral severe ptosis, bilateral brow suspension was performed either with stored fascia lata or Mersilene, or with autogenous fascia lata depending on the length of the patient's thigh. Asymmetric ptosis with pupil cover was treated with brow suspension if the levator function was less than 5 mm and with levator resection if better.

## Discussion

Blepharophimosis was first reported in 1841 by von Ammon.[1] The syndrome was subsequently described, and various methods of treatment to improve the cosmetic appearance have been advocated.[2-5] The reports, however, made no reference to the presence or absence of amblyopia or strabismus. Although Allen mentions these in discussing eyelid surgery, their incidence and

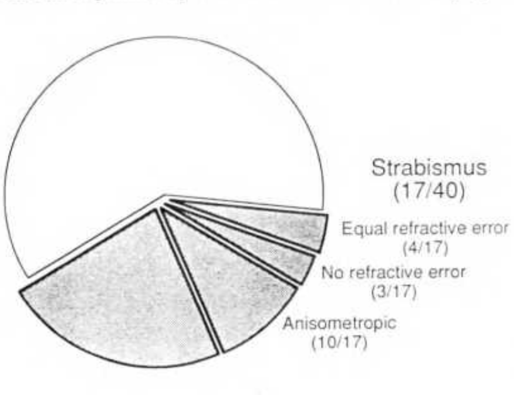

Figure 4 Moderate bilateral ptosis, 40 cases of 101.

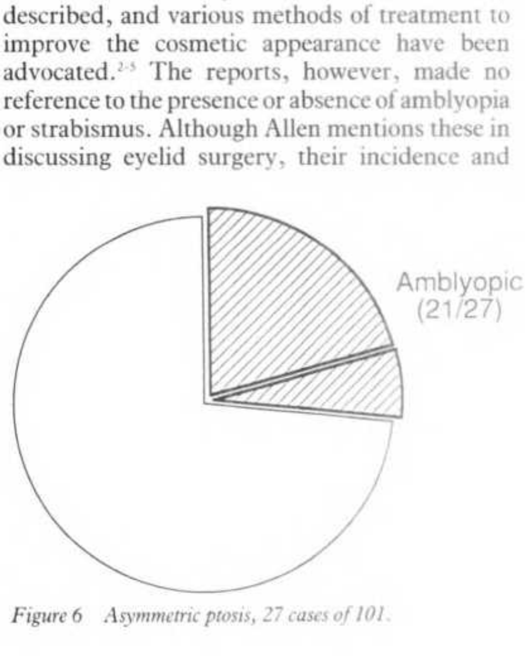

Figure 6 Asymmetric ptosis, 27 cases of 101.

management are not described.[6] We have therefore examined those cases of blepharophimosis presenting to us for oculoplastic opinion, with a view to determining the incidence of amblyopia and strabismus and the factors that may contribute to their cause.

Thirty one of 101 cases (30·7%) had a family history of blepharophimosis with a 5:1 predominance of inheritance through the father. This corroborates the finding of relative infertility of women with this condition.[7]

Amblyopia was found in a total of 56·4% of cases (57 of 101). 18·8% (19 of 101) had bilateral amblyopia with best corrected visual acuity of 6/12 or less and severe bilateral ptosis. 57·9% of these (11 of 19) had either equal or anisometropic refractive error and the remaining 42·1% had no error. 16·8% (17 of 101) were strabismic amblyopes with moderate bilateral ptosis. 20·8% (21 of 101) had asymmetric ptosis and unilateral amblyopia. This emphasises the risk of development of amblyopia due to ptosis.

Strabismus was found in 26·7% of cases (27 of 101). Of these 51·9% (14 of 27) were anisometropic, 22·2% (6 of 27) had equal refractive error, and the remaining 25·9% (7 of 27) had none, showing that refractive error is only partially responsible for squinting in these patients.

Moderate telecanthus of less than 35 mm was found in 71·3% of cases (72 of 101) and the remainder (29 of 101) had severe telecanthus of 35 mm or more. Asymmetry of the telecanthus of more than 2 mm was unusual (3 of 101). One case had an asymmetry of 7 mm with dense amblyopia and a convergent squint on the affected side but no refractive error and a clear pupillary axis. In the group with severe bilateral ptotic amblyopia (19 of 101) five had severe telecanthus with convergent squint but no refractive error. It is not possible to say whether telecanthus as such contributed to the squint and amblyopia, as these patients also had severe bilateral ptosis. However, we do not consider that the correction of telecanthus is indicated to prevent amblyopia or squint. Indeed telecanthus greater than 35 mm was found in 48·3% (14 of 29) of cases with no squint or amblyopia.

The indications for early ptosis surgery included bisection of the pupillary axis (with or without abnormal head posture), particularly if unilateral or if the child failed to make the effort to lift the lid; the development of intermittent strabismus; objection to occlusion treatment; or if tests show suppression to base out 4 and 15 dioptre prisms. However, these tests failed to identify those at risk of amblyopia in the severe bilateral ptosis group.

The most surprising finding was the high incidence of amblyopia and strabismus in this group. It had been presumed in the past that, since the ptosis was bilateral and approximately equal, these patients were not at risk of amblyopia. The second group with a more moderate degree of bilateral ptosis had a lower incidence of amblyopia and squint (42·5% – 17 of 40); but despite the higher incidence of anisometropia in those who developed a squint (58·8% – 10 of 17) there was still a significant number of patients (41·2% – 7 of 17) who were amblyopic with a squint and no anisometropia. The 21 patients with asymmetric ptosis in whom the pupil of one eye was intermittently covered were all amblyopic, but none had squints. These findings clearly indicate the importance of the ptosis and lid level in amblyopia associated with the blepharophimosis syndrome. We consider therefore that ptosis surgery should be carried out more readily and at an earlier stage than has been previously advocated.

The unoperated cases presenting in adulthood with bilateral ptosis were bilaterally amblyopic, whereas those children who underwent surgery early did better. Of our paediatric cases 74% (20 of 27) underwent surgery prior to reaching their fourth birthday but only three developed strabismus (only one with amblyopia), and two had amblyopia without strabismus. This emphasises the preventive advantage of appropriate early surgery.

We did not find the degree of epicanthic folds significant in relation to squint and amblyopia, but it is difficult to judge results objectively as there is no standard method of measuring them. This is in contrast to telecanthus, which lends itself well to accurate measurements, but the extent did not appear relevant to squint or amblyopia unless the telecanthus was asymmetrical. The moderate cases of epicanthus were treated with a Y-to-V plasty, whereas the more severe cases were lengthened with a double Z plasty.[8] At the same time the telecanthus was corrected with a medial canthal tendon shortening or transnasal wiring as appropriate.[8, 9]

The correction of the epicanthic folds is probably cosmetic. We found only one case of severe asymmetric telecanthus with epicanthic folds in which there was no other obvious cause for the amblyopia, as there was no ptosis and no refractive error.

## CONCLUSIONS

In our series of 101 cases of blepharophimosis syndrome the risk of amblyopia for whatever reason, single or combined, was more than half. The risk was highest if the ptosis was asymmetrical with pupillary axis embarrassment but was also present if the ptosis was bilateral. The effect of severe or asymmetric epicanthic folds seems to have little bearing on the normal development of binocular single vision. The innate desire to develop and maintain binocular single vision is strong but relatively short-lived. In cases of blepharophimosis syndrome we advocate careful regular orthoptic follow-up with early ptosis surgery where necessary.

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CASE REPORTS

# Neurilemoma of the caruncle: a clinicopathological report

I G Rennie, M A Parsons, M T Benson

**Abstract**

**We report a case of a neurilemoma (schwannoma) arising from the lacrimal caruncle. The clinical and light and electron microscopic features are described.**

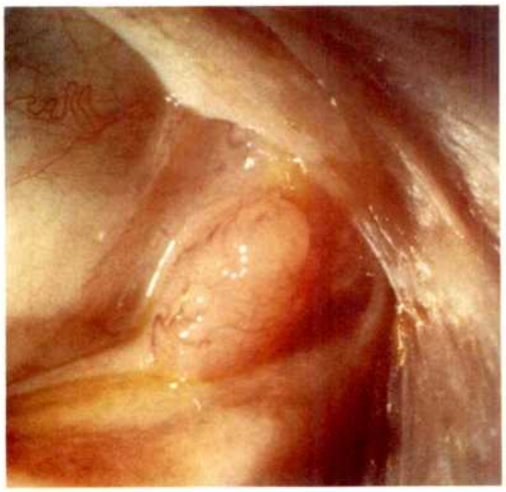

*Figure 1 Neurilemoma arising from right lacrimal caruncle.*

Neurilemomas (schwannomas) are benign, encapsulated, slowly progressive tumours that arise from peripheral nerves. They are usually solitary, occur principally between the ages of 20 and 50 years, and have a predilection for the head and neck.[1] In contrast to neurofibromas, neurilemomas are only occasionally associated with neurofibromatosis.[2]

Neurilemomas account for approximately 1% of biopsies for orbital tumours.[3] Intraocular lesions, presumably arising from the ciliary nerves, have been described infrequently.[4-7] We describe the clinicopathological appearances of neurilemoma arising from the lacrimal caruncle. To our knowledge this is the first reported case of such a lesion arising from this location.

## Case report

A 75-year-old female presented to the Ophthal-

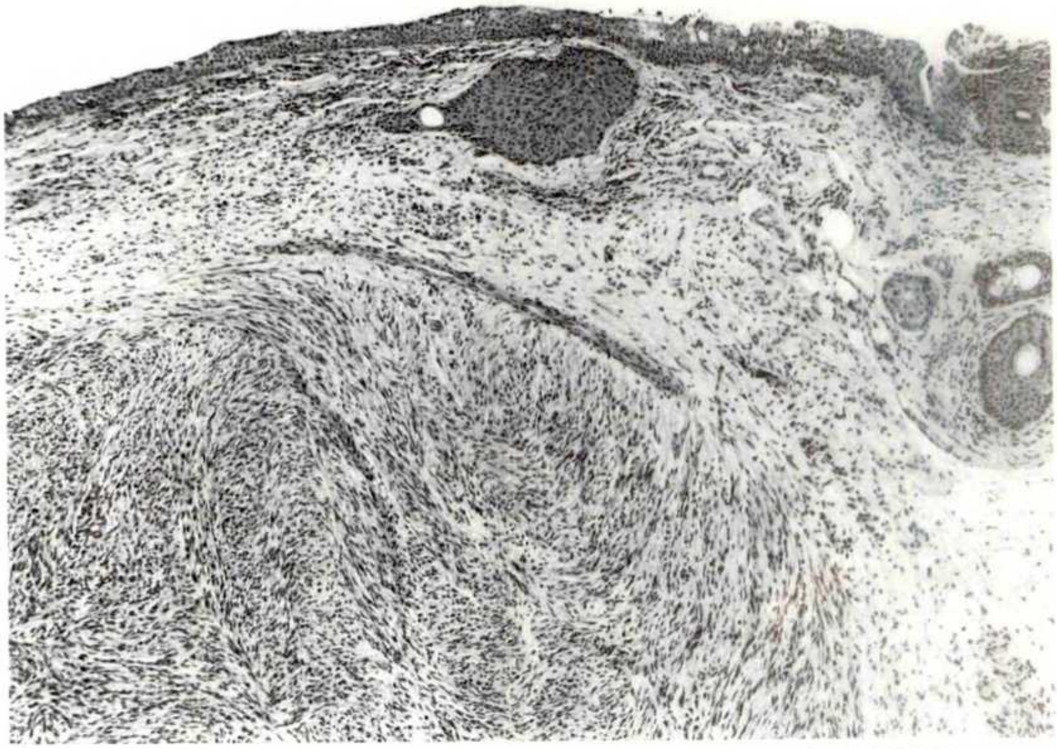

*Figure 2 On light microscopy the spindle cell neoplasm lies beneath the epithelium of the caruncle. A hair follicle is present at the right edge of the section. (Haematoxylin and eosin, × 160.)*

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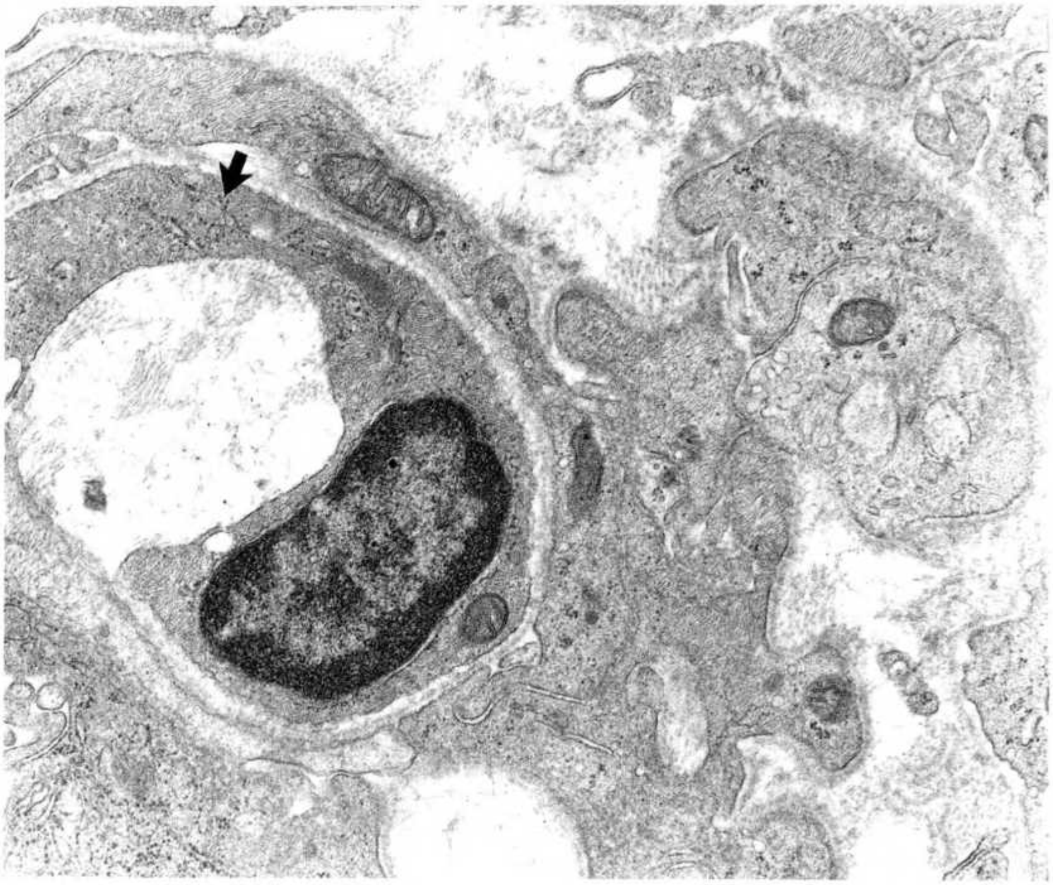

*Figure 3* Electron micrograph showing numerous complex interdigitating cell processes (right). On the left cellular process (arrow) is wrapped around extracellular collagen to form a pseudomesaxon. (× 20 000.)

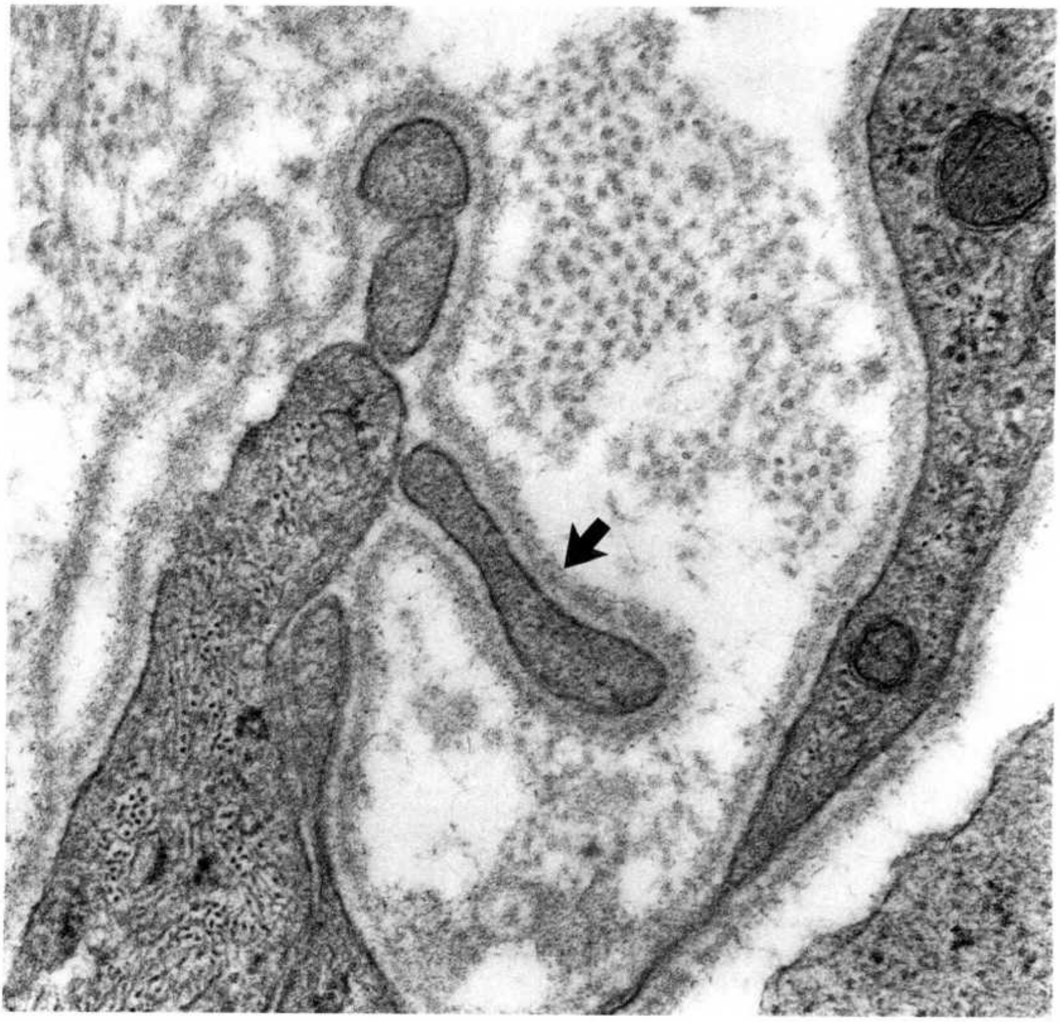

*Figure 4* An electron micrograph showing complex cellular processes surrounded by a prominent external lamina (arrow), with some redundant folds. (× 57 000.)

mology Department with a swelling arising from the right lacrimal caruncle. The patient was uncertain as to how long the lesion had been present. There was no significant ophthalmic history or evidence of neurofibromatosis. She had recently been diagnosed as suffering from an inoperable carcinoma of the pancreas.

On examination her best corrected visual acuities where right eye 6/12, left 6/12. A small, fleshy, oval lesion measuring approximately 6×4×4 mm was noted arising from the right lacrimal caruncle (Fig 1). The rest of the ocular examination gave normal results apart from pseudoexfoliation in the left eye and bilateral, mild, age-related macular changes. The lesion was removed under local anaesthetic. Her post-operative progress was uneventful.

### HISTOLOGICAL EXAMINATION

*Macroscopic findings.* The specimen consisted of a smooth lobulated yellow lesion measuring 6×4×4 mm, which on sectioning was encapsulated and had a homogeneous yellow cut surface.

*Microscopic findings.* On light microscopy there was a spindle cell neoplasm beneath the epithelium and hair follicles of the lacrimal caruncle (Fig 2). The tumour had a central cellular area, with a more myxoid peripheral zone of low cellularity. It was slightly fasiculated, but nuclear palisading was absent. Mitotic figures were not seen.

On electron microscopy the spindle shaped tumour cells had numerous complex interdigitating processes; in some cells these processes wrapped around extracellular collagen to form pseudomesaxons (Fig 3). The cells had a prominent external lamina with some redundant folds (Fig 4). Luse bodies of long-spacing collagen and occasional proteoglycan particles were present in the intercellular matrix. The electron microscopic appearances were characteristic of a neurilemoma (schwannoma),[8] and the light microscopic features were those of a benign neurilemoma.

## Discussion

The lacrimal caruncle is a piece of modified skin, covered by stratified squamous epithelium and containing hair follicles, sebaceous glands, and sweat glands.[9] It is innervated by a branch of the infratrochlear nerve. Neurilemomas arise as proliferations from the peripheral nerve sheath, and presumably this lesion developed from one of the terminal branches of the infratrochlear nerve.

Lesions of the lacrimal caruncle are relatively rare. In a review of 40 000 ophthalmic pathology specimens Luthra *et al* found only 112 (0·28%) lesions affecting the caruncle.[10] Shields *et al* reviewed over 18 000 pathology reports and found only 57 involving caruncle.[11] In these two studies papillomas and naevi accounted for over half the total lesions. Neither study identified a lesion arising from a peripheral nerve. Similarly, earlier reports by Evans,[12] Wilson,[13] and Serra[14] failed to identify a tumour of peripheral nerve as a cause of a caruncular lesion. It would appear that neurilemomas represent a rare and until now unreported form of caruncular tumour.

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*British Journal of Ophthalmology*, 1991, 75, 752

# Intraocular lens in a fighter aircraft pilot

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## Abstract

**A pseudophakic pilot of the Israeli air force flying an F-15 (Eagle) aircraft was followed up for three years. He experienced about 100 flying hours, 5% of the time under high *g* stress. The intraocular lens did not dislocate and no complications were observed. It seems that flying high performance fighter aircraft is not contraindicated in pseudophakic pilots.**

In the past the development of cataract has ended a pilot's flying career. Aphakic glasses cause a 33% magnification of objects and a severe visual field restriction; they are thus unsuitable in the flight environment. Contact lenses have the potential complications of a foreign body in the eye and are limited by a variable ocular tolerance and wearing time. Dust and particles floating around, wind blast, possible loss, and the nuisance of removing, cleaning, and reinserting make the contact lens less than ideal for the military environment. There are few data on pseudophakic pilots. The largest series deals with 75 commercial and private pilots.[1] In 1987 Mader *et al* reported that only eight pilots in the USA army (all of them flying helicopters) had an intraocular lens (IOL).[2] To the best of our knowledge this is the first report of an IOL implantation in a pilot flying high performance fighter aircraft and exposed to high *g* forces.

## Case report

A 34-year-old F-15 (Eagle) pilot underwent an extracapsular cataract extraction ECCE+IOL (Rayner-850B) implantation in the posterior chamber in March 1988. The operation and postoperative course were uneventful. Three months after the operation the patient resumed flying and was exposed to gradually increasing acceleration forces of up to +9 *g*. Four months after the operation he returned to full flight status. During three years of follow-up the pilot experienced about 100 hours of flying the high performance fighter aircraft, 5% of the time under acceleration forces of up to +9 *g*. On the last examination the patient's uncorrected visual acuity in his right eye was 6/18, and with a correction of (−2·25/+1·5×90°) reached 6/4. Stereoscopic and colour vision were undisturbed. The IOL was well centred, lying in the capsular bag, and the posterior capsule was clear and intact. In the left eye the visual acuity was 6/6, with an unaided near vision of Jaeger 1. No complaints or difficulty in flying have been noted.

*Table 1 Summary of reports on IOL implantation in pilots*

| *Author* | *Aircraft* | *No.* | *Type* | *Complications* |
|---|---|---|---|---|
| Mader *et al*[2] | Helicopter pilots | 8 | Ant. chamber-2 | Glare, erythropsia |
| | | | Post. chamber-5 | Glare, erythropsia |
| | | | Iris supported-1 | Cystoid macular oedema |
| Liddy *et al*[1] | Airline transport pilots | 6 | Not reported | Glare, altered colours |
| | Commercial pilots | 5 | | |
| | Private | 38 | | |
| | Flight engineer | 1 | | |

## Discussion

The reported cases of IOL implantation in pilots are summarised in Table 1. The largest series is of private and commercial pilots[1] in whom the main problem is loss of accommodative ability, necessitating near correction. In pilots of high performance fighter aircraft the vibration and acceleration which generate high gravitational forces cause an additional risk of IOL dislocation. To the best of our knowledge the safety of IOL implantation in high *g* aviators has not been reported. As to hard contact lenses, it was found that a significant hazard exists owing to the risk of decentration and dislodgement from the eye.[3] Soft contact lenses on the other hand were not found to be subject to decentration.[3-7] On a human centrifuge Forgie and Meek[6] tested soft contact lenses up to +6 *g* and found small amounts of decentration which they believed would not interfere with vision. Also on a human centrifuge Brennan and Girvin[7] found that soft contact lenses were displaced by a maximum of 1·5 mm when exposed to acceleration forces of +4 *g* and by 1·75 mm when exposed to +6 *g*. The decentration was more marked in soft toric lenses as a result of their heavier weight.

The effect of high *g* stress on IOLs has been studied only in monkeys by Tredici (personal communication). He implanted them in the anterior and posterior chamber of monkeys and exposed them to +12 *g* on a centrifuge. The IOLs did not dislocate and no complications were observed. These studies encouraged us to allow our patient to return to full flight activity.

It seems that flying high performance fighter aircraft is not contraindicated for pseudophakic pilots.

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British Journal of Ophthalmology, 1991, 75, 753–754

# Tranexamic acid-associated ligneous conjunctivitis with gingival and peritoneal lesions

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## Abstract

**A considerable number of agents have been proposed as causing ligneous conjunctivitis. We report the first case to arise as a side effect of tranexamic acid (Cyclokapron), an antifibrinolytic drug used in the treatment of menorrhagia. In addition to the typical conjunctival changes our patient had lesions affecting the gingiva and the peritoneum the last causing considerable protein loss into the peritoneal cavity.**

Ligneous conjunctivitis is a rare form of membranous conjunctivitis of unknown aetiology.[1] The disease classically presents with the appearance of thickened, 'wood-like' membranes covering the tarsal conjunctiva. Other mucus membranes may also become involved, including the middle ear, buccal mucosa, nasopharynx, larynx, vocal cords, trachea, vagina, and cervix.[1-4] We report a case of ligneous conjunctivitis in a young woman with Epstein's syndrome with involvement both of the gingiva and the peritoneum, caused by tranexamic acid (Cyclokapron).

## Case report

In March 1990 a 25-year-old Caucasian woman presented to the Bristol Eye Hospital with a nine-month history of ocular irritation and sticky discharge. On examination she had swollen eyelids with thickened, pale membranes adherent to the tarsal conjunctiva (Fig 1). Surgical debridement revealed the underlying conjunctiva to be hyperaemic and haemorrhagic, though it was rapidly coated as the membranes reformed. She also had generalised gingival hyperplasia with shallow ulcers predominantly at the gingival margin (Fig 1). Her ears, nasopharynx, larynx, vagina, and cervix were normal.

Three years earlier a diagnosis of Epstein's syndrome had been made after she presented with thrombocytopenia, nephropathy, and sensory deafness. Subsequent renal failure had necessitated peritoneal dialysis. On presentation, systemic drug treatment including daily pindolol 40 mg, enalapril 5 mg, indoramin 150 mg, sotalol 40 mg, alfacalcidol 0·25 mg, tranexamic acid 3 g, and erythropoietin 1500 units twice weekly. The tranexamic acid had been instituted in June 1989 to control menorrhagia. No other drug therapy had been started during the course of her disease.

Histological examination of the conjunctival membranes revealed masses of fibrin with collections of inflammatory cells, plus islands of entrapped epithelial cells (Fig 1). Gingival biopsy revealed hyperkeratosis and reactive thickening with ulceration and pronounced fibrin leakage, oedema, and fibrosis (Fig 1).

Over the following three months topical ocular

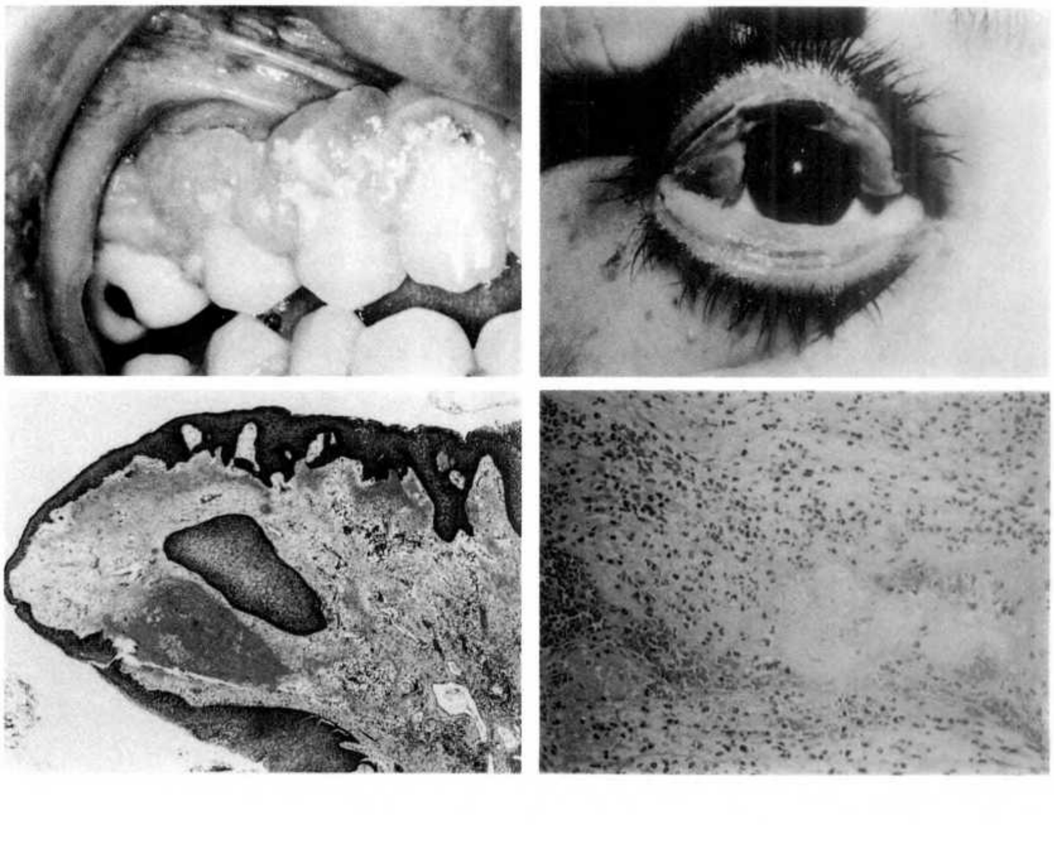

*Figure 1 Top left: Gingival hyperplasia with ulceration. Bottom left: Photomicrograph of gingiva, illustrating hyperkeratosis, ulceration, and fibrin deposition. (H-E, ×35.) Top right: Fibrinous membrane adherent to tarsal conjunctiva. Bottom right: Photomicrograph of membrane, showing amorphous fibrinous mass, with entrapped inflammatory cells. (H-E, ×265.)*

treatment included antibiotics, corticosteroids, cromoglycate, hyaluronidase, heparin, and cyclosporin. None of these induced any notable improvement.

Throughout this period she suffered a progressively increasing loss of protein into her peritoneal dialysis fluid, which became viscous and occasionally clotted. Quantitative analysis revealed a protein concentration of 0·62 g $\mathrm{l}^{-1}$, with a daily output of up to 2·48 g. Her serum total protein fell to 49 g $\mathrm{l}^{-1}$ and her albumin to 20 g $\mathrm{l}^{-1}$ causing her to become oedematous and to require albumin infusions. She further developed bilateral corneal ulcers, which proved refractory to treatment and healed only after prolonged occlusion.

In June 1990 all systemic drug treatment was discontinued, since a drug reaction was considered possible. Three weeks later the conjunctival membranes began to disintegrate, and over the subsequent 10 to 14 days they disappeared altogether. Over this same period her peritoneal protein loss resolved, her serum albumin rose to 39 g $\mathrm{l}^{-1}$, and her gingiva returned to normal health.

In September 1990 a recurrence of petechial bruising led to the reintroduction of tranexamic acid treatment. After a total dose of 6 g given over two days the lesions began to form again. No other new drug treatment was instituted at this time. Discontinuation again resulted in full resolution, and in the absence of tranexamic acid her eyes, mouth, and peritoneum have remained healthy.

## Discussion

Von Graefe first referred to ligneous conjunctivitis in 1854, though it did not acquire the distinctive name until 1933.[5] Since that time various aetiological agents have been proposed, including trauma, autoimmune phenomena, hypersensitivity reactions, bacterial or viral infections, and hereditary influences.[1] The underlying pathological abnormality probably involves a vasculopathy with increased vessel permeability and consequent protein loss, mainly fibrin.[1] Such a process has not been reported to involve either the peritoneum or gingiva.

Epstein's syndrome was first described in 1972 as a variant of Alport's syndrome,[6] a dominantly inherited disorder in which nephritis is associated with sensorineural deafness. Epstein's syndrome includes these features in association with thrombocytopenia. Recognised ocular features (of Alport's syndrome) include retinitis pigmentosa, cataract, lenticonus, and spherophakia. Ligneous conjunctivitis has not been reported.

In this case the association between ligneous conjunctivitis and exposure to systemic tranexamic acid was confirmed when the condition resolved, recurred, and subsequently resolved during two cycles of drug treatment. Recognised adverse effects of tranexamic acid include a tendency to intravascular clot formation, including stroke.[7] Ocular side effects include central retinal artery occlusion[8] and defects in colour vision. High doses in dogs cause retinal degeneration.[9]

The role of tranexamic acid in the aetiology of ligneous conjunctivitis is not apparent. It is possible that a pre-existing vasculopathy resulted in extravascular deposition of fibrin, the lysis of which was subsequently inhibited by the antifibrinolytic effect of tranexamic acid. A second postulate could include the tranexamic acid functioning as an antigen or a hapten, with subsequent antigen-antibody complex deposition resulting in complement-mediated vascular endothelial damage and consequent fibrin leakage.

Because tranexamic acid cannot be the aetiological factor in most cases of ligneous conjunctivitis, however, the present case would suggest that this condition may be the clinical expression of a variety of pathological insults.

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# Use of leeches in a case of severe periorbital haematoma

M J Menage, G Wright

## Abstract

**A case of severe penetrating eye injury and resulting periorbital haematoma is described. Leeches applied to the eyelids enabled examination of the globe to be carried out and improved the surgical approach. Leeches provide a speedy and efficient means of reducing a periorbital haematoma.**

Leeches have been used clinically for over 2500 years to treat a wide variety of medical conditions, often without any rational explanation, and so leeching has become associated with medicinal quackery. In recent years there has been resurgence of interest in leeches among plastic surgeons who use them, because of their superb decongestant properties,[1-3] to treat venous congestion in otherwise unsalvable skin flaps and tissue replants. Their use in periorbital haematoma has been described[4] but is probably not widely known among ophthalmologists.

## Case report

A 49-year-old alcoholic woman presented with a history of a fall during a heavy drinking session some 12 hours previously. She had been carrying a wine glass and had fallen on to the broken glass with her face.

Examination revealed a deep jagged laceration in the left eyebrow with gross lid and periorbital swelling, which prevented adequate examination of the globe. Penetrating injury was suspected, and it was deemed unwise to use excessive force to separate the tense lids, as this might result in expression of intraocular contents through any laceration of the globe.

Intravenous antibiotics were begun and the eyebrow wound was sutured. A large piece of glass was shown in the orbit on CT scan, but the extent of ocular damage could not be clearly seen.

Six leeches were applied to the patient's eyelids (Fig 1). They rapidly reduced the lid and periorbital swelling, and within a few hours the lids could be gently opened, revealing an intact cornea and a total hyphaema. Surgical exploration soon afterwards showed the globe to have been transected equatorially by a large piece of glass, and a primary enucleation was performed.

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25 April 1991

## Discussion

The case described is only one example of the ophthalmic use of leeches. Even relatively minor trauma can result in periorbital swelling severe enough to close the affected eye for several days. This is a considerable handicap to the patient which can delay a return to work or other activities. Treatment with leeches provides an easy, rapid, and highly efficient means of reducing the periorbital swelling and restoring visual function.

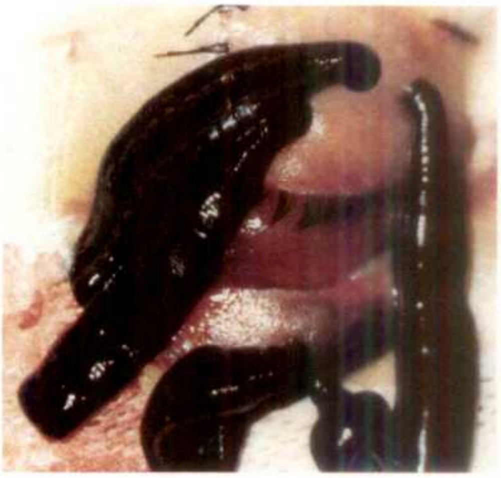

*Figure 1 Application of leeches to the swollen eyelids.*

Leech salivary secretions contain a unique and potent anticoagulant called hirudin, a histamine-like vasodilator that promotes local bleeding, a local anaesthetic, and hyaluronidase that promotes the local spread of the other leech salivary secretions into the bite.[2] A leech can remove up to 15 ml of blood in a single meal, and the bite can continue to bleed for several hours if a dressing is not applied.

The site for leech application should be cleansed with saline to remove all ointments, dried blood, antiseptics, and so on, because these may discourage the leech from biting. The leech should be gently handled with protective gloves, and a drape with a small central hole can be used to direct the leech to the desired area for treatment. Milk or 5% glucose from a syringe will encourage a reluctant leech to take hold. The leech will usually take between 20 and 40 minutes to finish its meal at which time it will fall off the skin. Leeches can be used again on the same patient, but because of the risk of transferring blood-borne infection are not used again for other patients. They are killed by immersion in 70% alcohol.

The bacterium *Aeromonas hydrophilia* lives symbiotically in the gut of the leech. It is recommended that the leech should not be squeezed to remove it forcibly from the patient because to do so may inoculate its stomach contents into the wound. Infections with this organism have been described after leech therapy[5] but are rare. If necessary the leech can be forced to relinquish its hold by application of salt or by stroking with an alcoholic wipe.

*Hirudo medicinalis* is the commonly used species of leech in both Britain and the USA, and is reared on specialist leech farms. If required, stockists will dispatch a consignment by express delivery. In hospitals with large plastic surgery departments, where leeches are sometimes used, the pharmacy will keep a small stock available for immediate use. They are easily kept in a muslin covered glass or plastic tank of water at 20°C and will live up to a year without feeding provided the water is changed regularly.

The leeches were obtained by express delivery from Biopharm, a leech farm in Swansea.

We thank Mr J Thomsitt for permission to report on this patient and Ms Karen Jones for photography.

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# FIFTY YEARS AGO

## A Fifteenth Century English translation of John of Arderne's *de Cura Oculorum*

By R R James, Woodbridge

John of Arderne was the first of a long line of celebrated English surgeons. He was born in 1307 and was in practice at Newark-on-Trent from 1349 to 1370. In the latter year he moved to London and in 1377 he wrote his booklet which forms the subject of this paper. We do not know the date of his death, nor do we know where he learnt his art. In one of his writings he describes himself as 'chirurgus inter medicos', and in another as 'cirurgicorum minimus'; but he was evidently in extensive practice and his writings cover a very large field. Perhaps his best work was on fistula-in-ano, piles and rectal cancer. This displays great powers of observation and is well documented with case records. It is decidedly original. The same cannot be said of his treatise on the cure of the eyes; it is for the most part a compilation from the work of others, notably Lanfranc. Ophthalmologically it is worthless, but not without interest.

A precious oynement for bleryed yene and watery. Take a clene holowgh basyne & anoynt it with inne with buttere dat is not salt and afterward whelve de basyne uppone a vessell dat a mannys uryne is inne, tarte & hote & so let it stande stylle tyll it be colde. Afterward that schalbe taken dat clevyd withinne to de basyne de weche is blewysshe of colour & ther schalbe putte therto a litill of de grece of a caponne & des schalbe wele medlyd togydere ayene de sounne & thanne boxe it.

With dis oynement de yelydys schulbe anoyntyd mediocrely with a lytyll slice at eve whane he goth to bedde & bynde it with a bonde tylle one de morowe.

This oynement cureth beste above alle de medicines in de wordle de bleryed yene & de waterynge yene as wele in crokedmen as in oder, de weche I have often tymes provyd *per certo*. And after Johannem Damascenum in alle de sorowe of de yene & ayenst defawte of de syghte ffurste it behoveth dyligently to consydre wheyther it be of hote cause or of colde, & yf it be of hote cause furste de mater scalbe deffyed *cum surupo acetoso* III dayes or IIII. And whanne de mater is dygeste ther schall thane be yoven furste a clystere mollificatyff de mor*.

That schall devoyd all de body & dat schall be done with $\frac{v}{2}$ ·1· of de a lectuarye made of de juse of rosys & made scharpe with Dyagredye. And thanne thou mayst sywerly werke with diverse remedyes in de seyd places after that de semeth to spede.

In colde cause de mater also schall furste be deffyed cum oximell diuretico i squillitico & thane ferdermore de clysterye schalbe yoven as it is aforseyde & by de morowe alle de body schalbe purgyd cum $\frac{v}{2}$ from Jorapige Gale†. And afterwarde he schall procede foorth sywerly to de places of remedy & spede wele . . .

Here ends the Ms. of the cure of the eyes.

†The hierapicra of Galen.

To my regret I have not been able to compare the proof with the original, and so some errors in 15th century spelling have probably crept in.

*Br J Ophthalmol* 1941; **25**: 526–35.

# VOLUME 75 · AUTHOR INDEX

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